UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

CIRCULATORY SYSTEM DEVICES PANEL

+ + +

April 26, 2012
8:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PANEL MEMBERS:

WARREN LASKEY, M.D.	Temporary Panel Chair
DAVID C. NAFTEL, Ph.D.	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
RICHARD A. LANGE, M.D.	Temporary Voting Member
PATRICIA KELLY, M.D.	Temporary Voting Member
DAVID MILAN, M.D.	Temporary Voting Member
GREGORY DEHMER, M.D.	Temporary Voting Member
PAMELA E. KARASIK, M.D.	Temporary Voting Member
RALPH BRINDIS, M.D.	Temporary Voting Member
DEBRA GATES McCALL	Patient Representative
BURKE T. BARRETT, B.A., B.S., M.B.A.	Industry Representative
ROBERT DUBBS, J.D., M.B.A.	Consumer Representative
JAMIE WATERHOUSE	Designated Federal Official

FDA REPRESENTATIVES:

BRAM D. ZUCKERMAN, M.D.
Director, Division of Cardiovascular Devices

MICHELLE BOLEK
Press Contact

FDA PRESENTERS:

DORIS TERRY, M.S., M.B.A.
Pacing, Defibrillator and Leads Branch
Division of Cardiovascular Devices
Office of Device Evaluation

CDR BRIAN LEWIS, M.D., USPHS
Division of Cardiovascular Devices
Office of Device Evaluation

YAO HUANG, M.S.
Division of Biostatistics
Office of Surveillance and Biometrics

SHAOKUI WEI, M.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Biometrics

FDA ADVISORS:

MITCHELL SHEIN, M.S.
Branch Chief, Pacing, Defibrillator and Leads Branch
Office of Device Evaluation

ERIN CUTTS, B.S.
Office of Device Evaluation

KIM SELZMAN, M.D.
Office of Device Evaluation

SPONSOR PRESENTERS:

JON HUNT, Ph.D.
VP, Clinical & Regulatory Affairs
Cameron Health, Inc.

MICHAEL R. GOLD, M.D., Ph.D.
Michael E. Assey Professor of Medicine
Director of Cardiology
Medical University of South Carolina

MARTIN C. BURKE, D.O.
Professor of Medicine, Interim Chief, Section of Cardiology
Director, Heart Rhythm Center
University of Chicago

ALAN MARCOVECCHIO, M.S.E.E.
Director, Clinical & Regulatory Affairs
Cameron Health, Inc.

SPONSOR ADVISORS:

ANDREA RUSSO, M.D.
Director of Cardiac Ablation and Arrhythmia Services
Cooper University Hospital

MARK S. KREMERS, M.D.
Cardiac Electrophysiologist
Mid Carolina Cardiology

OPEN PUBLIC SPEAKERS:

LISA WILLIAMS
S-ICD Device Recipient

INDEX

INDEX

M E E T I N G

(8:00 a.m.)

DR. LASKEY: I'd like to get us started, it being 8:00 as Dr. Zuckerman pointed out. I'd like to call this meeting of the Circulatory System Devices Panel to order.

I'm Warren Laskey, the Chairperson today. My day job is the Chief of Cardiology at the University of New Mexico.

I'd like to go around the table, beginning with Dr. Zuckerman, and if you could please state your position and affiliation.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. NAFTEL: My name is David Naftel. I'm a Professor of Surgery and Biostatistics at the University of Alabama at Birmingham.

DR. MILAN: I'm David Milan. I'm a clinical cardiac electrophysiologist at Massachusetts General Hospital in Boston.

DR. KARASIK: I'm Pamela Karasik. I'm the Acting Chief of Cardiology at the VA here in Washington, D.C.

DR. KELLY: Patricia Kelly. I'm an electrophysiologist in Missoula, Montana.

DR. DEHMER: Gregory Dehmer. I'm a Professor of Medicine at Texas A&M College of Medicine and Chief of Cardiology at the Scott & White Clinic in Temple, Texas.

DR. SOMBERG: Good morning. I'm John Somberg. I'm a Professor in Medicine and Pharmacology at Rush University in Chicago.

DR. LANGE: I'm Rick Lange, Professor and Vice Chairman of Medicine, University of Texas, San Antonio.

DR. BRINDIS: Ralph Brindis. I'm the Senior Advisor for Cardiovascular Disease, Northern California Kaiser Permanente, and a cardiologist.

MS. McCALL: Debra McCall, StopAfib.org, and I'm the Patient Representative.

MR. DUBBS: Bob Dubbs, Consumer Representative, retired.

MR. BARRETT: Thank you, and bringing up the rear, yes. Okay.

MR. BARRETT: Good morning. My name is Burke Barrett. I'm the Vice President of Regulatory and Clinical Affairs for CardioFocus. I'm the Industry Rep on this Panel, and I'm the guy who didn't get his wakeup call this morning. I apologize.

DR. LASKEY: Welcome. I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations and vote on information related to PMA P110042 for the Cameron Health Subcutaneous Implantable Cardioverter Defibrillator

System.

If you've not already done so, please sign the attendance sheets that are on the tables outside, and I'll turn things over to Jamie Waterhouse, the Designated Federal Officer for the Circulatory Devices Panel who will make some introductory remarks.

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The Food and Drug Administration is convening today's meeting of the Circulatory Systems Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

The FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws.

Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on the information related to the premarket approval application for the Subcutaneous Implantable Cardio Defibrillator System sponsored by Cameron Health. The S-ICD is the first implantable defibrillator that does not require the implantation of an electrode, either on or in the heart. The S-ICD is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias. The device is capable of delivering high energy defibrillation shocks as well as bradycardia demand mode cardiac pacing. The study provides data from the treatment of induced acute and chronic episodes of ventricular tachycardia/ventricular fibrillation and spontaneous episodes. In addition to the investigational device exemption study, clinical data were also obtained from studies outside the United States and registries.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208 and Section 712 of the FD&C Act.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Mr. Burke Barrett is serving as the Industry Representative, acting on behalf of all related industry, and is employed by CardioFocus.

We would like to remind members and consultants that if the discussions involve any other products and firms not already on the agenda for which a FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting: Drs. Richard A. Lange, David Milan, Ralph Brindis, Gregory Dehmer, Patricia Kelly, Pamela Karasik.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Dr. Warren Laskey to act as Temporary Chairperson for the duration of this meeting.

This has been signed by Dr. Jeffrey Shuren, Director for Center for Devices and Radiological Health on April 12, 2012.

For the duration of the Circulatory System Devices Panel on April 26, 2012, Ms. Debra McCall has been appointed as a temporary non-voting member. For the record, Ms. McCall serves as a consultant to the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on April 20, 2012.

Before I turn the meeting back over to Dr. Laskey, I would like to make a few general announcements.

The transcripts of today's meeting will be available from Free State Court Reporting, Inc. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Michelle Bolek.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. James Clark at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and any other electronic devices at this time. Thank you.

Dr. Laskey.

DR. LASKEY: Thanks, Jamie. We are already ahead of schedule. This is great. Let's see if we can maintain this pattern.

So it being 8:15, I'd like to introduce the Sponsor for their presentation, proceeding with Sponsor presentation. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Welcome, Cameron Health.

DR. HUNT: Good morning. I'm Jon Hunt, the Vice President of Clinical and Regulatory Affairs at Cameron Health. On behalf of my colleagues and the investigators of the Cameron Health Subcutaneous Implantable Defibrillator System, I'm pleased to be here today.

We're here to share information on a major advance in the treatment of patients at risk of sudden cardiac arrest due to ventricular tachyarrhythmias. Cameron Health has dedicated itself to the development of subcutaneous implantable defibrillators since it was founded 11 years ago.

I'd like to begin briefly by explaining the device we're here to discuss and offer a brief overview of our presentation.

The device we're here to discuss is the Subcutaneous-ICD System. For purposes of this presentation, we will refer to this technology as the S-ICD System. The S-ICD System is similar in function to existing commercially available transvenous ICDs in that it is designated to sense, detect, and treat malignant ventricular tachyarrhythmias. It is the same defibrillation therapy delivered in a new way. The most notable difference is that unlike the transvenous ICD, which has leads placed intravascularly, the S-ICD System is entirely subcutaneous. The pulse generator and electrode are placed extrathoracically outside the ribcage. These distinctions have the potential to offer patients several clinically meaningful advantages while still providing effective, reliable, and safe conversion of life-threatening ventricular tachyarrhythmias.

The proposed indication for the device is listed on the slide. The system is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias. You will note that the system is not indicated for patients with symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing.

The S-ICD System is a result of more than a decade of development effort. Some notable milestones are included on this slide. Proof of concept began in 2001, and the system received its CE mark in July 2009. The patient enrollment in the IDE study began the following year. The PMA was granted expedited review status in June 2011 and submitted in December 2011.

To date, the S-ICD System has been distributed outside of the United States in 10 countries and has a combined worldwide experience of more than 1200 implants.

With that brief introduction, I would now like to introduce our presenters, two of whom are outside experts. They are paid consultants to Cameron Health and are being compensated for their time and travel here today. They do not hold an equity interest in the company.

Dr. Michael Gold, the Michael E. Assey Professor of Medicine and Director of Cardiology at the Medical University of South Carolina, and an investigator in the IDE trial, will discuss the problem of sudden cardiac arrest and its treatment. He then will provide an overview of the evolution of ICD technology with the introduction of Cameron Health's S-ICD System. Dr. Gold will summarize the initial testing of the system, both its preclinical and early clinical studies, and he will then outline the IDE clinical study design.

Next, Dr. Martin Burke, Professor of Medicine and Interim Chief of Cardiology, as well as the Director of the Heart Rhythm Center at the University of Chicago, and a study investigator, will walk us through the study results. As part of that discussion, he will address some of the specific topics FDA raised in its materials to this Panel, including infection, inappropriate shocks, discomfort, and battery longevity. He is uniquely qualified in that he treated nearly 12% of the patients enrolled in the IDE study.

Alan Marcovecchio, Director of Clinical and Regulatory Affairs at Cameron Health, will provide an overview of our training program and labeling, as well as our robust proposed postmarketing approval study which we're interactively working on with FDA.

Dr. Gold will then return to offer perspectives on the benefits and risks of the device and conclude our presentation.

In addition to the presenters, we have other experts with us today, which include individuals from the CEC, a biostatistician, and other investigators in the study to answer your questions.

Drs. Fogoros, Kremers, Lee, and Russo are on hand to address specific questions. Their affiliations are listed on this slide.

With these introductions, I'd like to thank the FDA review team and this Panel for its consideration of what we are convinced is a major advancement in treatment for patients with life-threatening ventricular tachyarrhythmias.

I'd now like to invite Dr. Gold to walk us through the problem faced by so many patients, their treatment options, and the S-ICD System technology and development program. Dr. Gold.

DR. GOLD: Thank you, Dr. Hunt. I'm Michael Gold, and I'm a practicing electrophysiologist at the Medical University of South Carolina in Charleston. I was an investigator in the IDE study for the S-ICD System, which we'll be presenting today. I've practiced in the field of electrophysiology for more than 20 years, and I've been involved in the development of testing of numerous implantable defibrillator systems.

The advent of ICDs was critically important for patients at risk for sudden cardiac arrest. Sudden cardiac death is a significant public health concern, is a leading cause of death in the U.S., responsible for nearly 1,000 deaths per day. In fact, sudden cardiac arrest claims more lives than lung cancer, breast cancer, and AIDS combined.

ICDs are proven to be 98% effective in treating ventricular tachyarrhythmias that can lead to sudden cardiac arrest. In contrast, without intervention, sudden cardiac arrest is fatal a vast majority of the time. Time is of the essence for patients experiencing cardiac arrest.

This chart shows there is approximately a 10% decrease in survival for every minute a patient remains in cardiac arrest. Multiple randomized post-approval clinical studies have proven the effectiveness of ICDs in preventing mortality.

One such study, the AVID study, a NIH-sponsored trial, showed significant reductions in all-cause mortality for patients implanted with ICDs versus antiarrhythmic drugs. The AVID study showed that ICDs are successful in reducing mortality in secondary prevention patients.

The SCD-HeFT study, also a NIH-sponsored trial, demonstrated the benefits of ICDs in primary prevention patients with heart failure. The analysis showed that ICDs reduced all-cause mortality by 23%.

These were two of the many studies that showed that ICDs save lives in both secondary and primary prevention patients.

While the fundaments of ICD therapy have remained largely unchanged, since being introduced in the United States in 1985, the technology has evolved significantly over the years. Early epicardial defibrillator systems required opening the chest with a sternotomy to place patches on the heart, as shown here on the left panel.

The next major advance in device design, pictured on the right, was a development of transvenous ICD systems to simplify the implantation procedure. Transvenous ICDs were first approved in the United States in 1992. With these systems, one or more leads are implanted intravascularly using fluoroscopy.

Despite the effectiveness of ICD systems, they do have limitations. We have grouped these into three broad categories, anatomical limitations, implantation risks, and explantation risks.

First, although relatively uncommon, certain congenital heart anomalies and other conditions prevent the use of transvenous leads.

Second, implantations of leads intravascularly is known to carry the risks of pericardial effusion, cardiac tamponade, perforation, pneumothorax, and lead dislodgement. In addition, the implantation procedure can cause systemic infections leading to endocarditis or sepsis. While these implantation complications occur relatively infrequently, the severity is high.

Finally, as demonstrated in the recent literature, complications are commonly caused by transvenous lead degradation and fracture. Removing or replacing leads carries risks, including vessel dissection, perforation, vein occlusion, valve damage, bleeding, tamponade, or even death.

As I mentioned, transvenous leads can fracture, dislodge, or their insulation can degrade.

Dr. Kleemann and colleagues reported in a cohort of 990 patients that transvenous leads have a failure rate of up to 10% at 5 years and that 20 to 40% of leads will fail over the course of their lifetime.

Since ICD patients now often have life expectancies measured in decades, rather than months or years, lead failure is a critical problem in long-term patient management.

The S-ICD System was designed to provide the proven benefit of defibrillation therapy without the need for transvenous leads, and therefore without many of the complications associated with such systems.

In contrast to traditional ICDs, the subcutaneous placement of the S-ICD System is designed to prevent the risk of pericardial effusion or tamponade and vessel perforation or valve damage, and without a transvenous lead, there is no direct pathway for microorganisms to reach the bloodstream.

Additionally, since the S-ICD System's electrode is implanted outside the vascular system and heart, it is not exposed to the stresses caused by the heart's 35 million contractions every year, a significant factor in the failure of transvenous leads.

Let me now briefly describe the components of the S-ICD System. The pulse generator is hermetically sealed and contains the electrical components that deliver defibrillation and post-shock pacing therapies as well as controlling the functionality of the device. It has an expected life roughly of 5 1/2 years under typical conditions. Importantly, at the time of implant, the pulse generator has a capacity to deliver over 100 full energy shocks.

The subcutaneous electrode is implanted beneath the skin along the sternum. Once the electrode is connected to the pulse generator, the electrode provides a pathway for cardiac sensing and defibrillation of the system.

The electrode insertion tool is a single use tunneling tool used to implant the electrode. We will show a video shortly demonstrating how this tool is used to position the electrode and where the final S-ICD System is located within the patient.

The handheld portable computer allows the physician to program and communicate with the system via wireless telemetry.

The difference in the placement of the transvenous ICD and Cameron Health S-ICD is shown on this slide. The transvenous ICD is shown on the left panel. Of note, the pulse generator of the transvenous ICD is located in the pectoral region. The lead is placed intravascularly with the tip in the right ventricle.

The S-ICD is shown on the right panel. With this system, the pulse generator is placed in the lateral subcutaneous tissue, and the electrode is placed under the skin, outside of the ribcage and parallel to the sternum. The primary evolutionary advance of the S-ICD System is the unique location of the pulse generator and electrode.

The electrode is designed with a central multi-strand cable core for strength rather than the hollow central lumen common to all transvenous ICD leads. This provides a significant design advantage contributing to the durability of the subcutaneous electrode. Because of the unique location, which is not subject to flexing or motion, a high durometer insulation material could be used.

Additionally, the unique placement of the S-ICD System electrode permits a one-size-fits-all electrode design. This one electrode length was used in all patients in the clinical study and was implanted effectively in patients weighing from 95 to 509 pounds.

Another unique feature of the S-ICD System is the use of a non-invasive preoperative screening tool which is a plastic template that is placed over a printed surface ECG. This tool allows physicians to assess the suitability of the S-ICD System implant based on a surface ECG.

The S-ICD System is implanted by first identifying the desired location for the pulse generator at the mid axillary line in the lateral thoracic region near the fifth or sixth intercostal space. After sterile preparation, an incision is made and the pulse generator pocket is formed. A second incision is made by the xiphoid. The EIT is tunneled from the xiphoid incision towards the device pocket and is then tied to the electrode with a long suture loop. The electrode is pulled to the xiphoid until the coil and proximal sense node are exposed and the suture sleeve is attached. The exposed electrode is used to measure for an incision that is made along the lateral sternal margin. The EIT is then used to tunnel the long suture loop from the xiphoid to the superior incision, and once exposed, the suture loop is cut and the EIT is removed from the xiphoid incision. The electrode is pulled from the xiphoid to the superior incision and fixation is made to the fascia. The electrode is connected to the pulse generator, which is subsequently inserted and secured into the pulse generator pocket. All incisions are closed, and the device setup commences using the programmer.

The S-ICD System works using three possible sensing vectors shown in the colored arrows on this slide. These sensing vectors can be automatically selected by the system or manually programmed by the physician. After implantation, the system is programmed for either single or dual zone therapy.

In single zone programming, the shock zone is based solely upon the patient's measured heart rate. In contrast, dual zone programming utilizes both the patient's heart rate and specific morphological criteria to determine the appropriateness of therapy delivery.

The decision to use a single zone or dual zone program in the IDE study was left to the physician's discretion.

During the implantation, ventricular fibrillation is induced, also referred to as induction testing, and a submaximal energy shock is delivered by the S-ICD System to convert the induced tachyarrhythmias and ensure the effectiveness of the therapy in the patient. While a submaximal shock is used in induction testing, the system's 80 J maximum energy shock is the only one available outside the hospital. The system will deliver up to five maximum energy shocks for any particular episode.

The S-ICD System can also deliver on-demand post-shock bradycardia pacing at a rate of 50 beats per minute for up to 30 seconds.

Additionally, the system will record and store up to 44 electrograms whenever a charge is initiated by the system, allowing the physician to later review the arrhythmias using the programmer.

With regard to longevity, the S-ICD System is designed to last over 5 years under typical usage assumptions, but at the time of implant, it is also capable of delivering over 100 full energy shocks for the less common circumstance where patients experience VT storm requiring frequent defibrillation shocks.

Now I will outline the development program for the S-ICD System. The S-ICD System has been in development for more than a decade. The system underwent comprehensive preclinical bench testing, including rundown testing on battery life, as well as acute and chronic animal studies with histology to ensure that it met all Cameron Health specifications and FDA-recognized standards.

As for initial human clinical studies, a series of acute within subject human studies were first performed to evaluate the feasibility of a subcutaneous defibrillator. Following feasibility confirmation, additional human studies were conducted to determine the optimal system configuration, which ultimately led to the S-ICD System configuration used in the IDE study.

Of equal importance was the early evaluation of the fully implanted S-ICD System. This initial chronic study collected data on six patients. The system achieved a 100% conversion rate and showed the long-term viability for the system.

The CE study provided additional support for the effectiveness and safety of the S-ICD System over six months' follow-up. This study was conducted with 55 patients and met all safety and effectiveness objectives.

Many important lessons were learned from these initial human clinical studies. These improvements to the surgical technique including the use of suture sleeves to yield more consistent electrode placement and stability. Additionally, there was important learning on the appropriate composition and side of the suture material and appropriate technique for insertion of the electrode pin into the header.

As a result of these initial human clinical studies, labeling was updated, and lessons learned were carried forward in the IDE trial.

With the preclinical and initial clinical overview, let's discuss the IDE study design. The IDE study's objective was to evaluate the effectiveness and safety of the S-ICD System in treating life-threatening ventricular arrhythmias. The IDE clinical investigation was a prospective, multicenter, single-arm study in the United States, Europe, and New Zealand.

A single-arm study design was mutually determined by Cameron Health and the FDA to be appropriate since the effectiveness of defibrillation therapy is well established.

Enrollment began in January of 2010 and concluded in May of 2011. Patients were included in this study who were over the age of 18 years and met ACC/AHA/HRS guidelines for implantation or replacement of an ICD, providing they had the appropriate preoperative ECG per the screening tool described previously.

Key exclusion criteria were documented spontaneous and frequent VT that were reliably treated with antitachycardia pacing, existing epicardial ICD patches or subcutaneous array in the left thoracic quadrant, unipolar pacemakers, and severe renal dysfunction.

Based on both the inclusion and exclusion criteria, the IDE study eligibility was broad in design to include a wide range of patients proving to benefit from ICD therapy.

The IDE study had two primary endpoints, one for effectiveness and one for safety. The primary effectiveness endpoint was the acute induced ventricular fibrillation conversion efficacy rate defined as two consecutive successes out of four contiguous attempts in the same shock polarity. This rate was evaluated by comparing the lower confidence bound of the observed rate to the prespecified performance criterion of 88%.

Induction testing provides a practical means to collect effectiveness data in contrast to spontaneous episodes that occur at rates of roughly 5% per year. For this reason, induction testing has historically been used in prior ICD clinical trials as the benchmark for effectiveness.

A complication-free rate has historically been used in predicate IDE and benchmark ICD studies as a measure of safety. As such, the primary safety endpoint for the IDE study was a complication-free rate at 180 days, evaluated by comparing the lower confidence bound of the observed rate to the performance criterion of 79%.

Moving to the study sample size, the sample size of the study was established to provide 80% power with an apriority significance level of 0.025 for each primary endpoint. Using an estimated VF conversion rate of 93%, and an estimated complication-free rate of 85%, assuming a 10% attrition rate for this type and duration of study, the final enrollment target of 330 patients was derived.

In addition to the primary endpoint, a number of secondary analyses were prespecified in order to provide a more comprehensive evaluation of the acute and chronic effectiveness and safety of the S-ICD System. Collection of data from non-IDE sources were prespecified to supplement the expected low occurrence rates of important measures such as spontaneous episodes of VT and VF. Time to therapy for induced episodes was examined, and freedom from complications was assessed at one year.

Finally, the IDE study included a variety of safeguards to ensure data integrity and patient safety. All data were entered into a secure electronic database by investigational sites, and every site was monitored to ensure the accuracy and completeness of the data.

Additionally, a clinical events committee was utilized to adjudicate all spontaneous episodes, clinical events, and deaths, and a data and safety monitoring board also provided safety oversight throughout the study duration.

Dr. Burke will now summarize the study and its results as well as some of these additional analyses.

DR. BURKE: Good morning. I am Martin Burke, and I am a practicing electrophysiologist, Professor of Medicine, Interim Chief of the Section of Cardiology at the University of Chicago, and Director of the Heart Rhythm Center.

As a transvenous lead extractor, extracting nearly 200 leads a year, I became very interested in becoming an investigator in the IDE study for the S-ICD System, in which I enrolled and treated 39 patients.

Today, I will be discussing the results of the S-ICD System IDE study. I will begin with a broad overview and then focus on the results for the primary clinical endpoints of effectiveness and safety. I then will discuss some additional data analyses that were performed.

The S-ICD System's IDE study involved 33 sites and 330 patients in four countries. The United States accounted for roughly 85% of the sites and patients in the study. The 33 participating sites included a broad spectrum of geographically dispersed facilities representing large academic teaching hospitals and private practice institutions. The implanting centers include major urban hospitals as well as smaller medical centers in traditionally underserved communities.

There were 330 patients enrolled in the IDE study. Nine patients withdrew prior to implantation for a variety of reasons ranging from an insurance denial to patients changing their minds after enrollment, leaving 321 patients in the safety cohort. Seventeen patients did not complete VF conversion testing at the discretion of the physician, resulting in an effectiveness cohort of 304 patients. Sixteen of the seventeen patients had non-evaluable results from incomplete testing, and one patient did not undergo acute VF conversion testing at all due to a persistent left ventricular thrombus.

After VF conversion testing, and during the follow-up period, a total of 27 patients exited the study. Seven were non-evaluable patients who had their systems explanted prior to hospital discharge. An additional 20 patients exited the study after hospital discharge.

There were eight deaths during the study. I will discuss the details of these later in the presentation.

Ten patients had their S-ICD Systems explanted. Four of these explants were due to infection, two for inappropriate shocks, and one for premature battery depletion. One patient was explanted due to a developed need to CRT-D system, and one patient was explanted in order to provide arrhythmia suppression by increasing heart rate with pacing following multiple storm events for ventricular arrhythmias.

Finally, one patient underwent an explant against medical advice of his physician for reasons unrelated to system performance.

Two patients withdrew from the IDE study. One of these patients withdrew for a heart transplant. The other patient withdrew consent because he was terminally ill.

The first data results I will discuss today involve the implant procedure itself. If you recall from Dr. Gold's presentation earlier, a key difference between the S-ICD System and transvenous ICDs is that the S-ICD System does not require the use of fluoroscopy during the implant procedure. When reviewing the data from the implant attempts in the 321 patient safety cohort, 95% of implants used anatomical landmarks only. Additionally, there was no S-ICD System electrode or pulse generator movement found in 99% of the implanted patients throughout the follow-up period.

Of the 314 patients discharged, with an S-ICD System, the mean follow-up for the study was 321 days, and the visit compliance throughout the duration of the study was excellent. The 180-day safety endpoint visit compliance rate was 99%.

The mean age for patients enrolled in the study was 52 plus or minus 16 years. 26% of the patients were female, which is consistent with clinical practice as supported by the NCDR Registry. Height, weight, and BMI demographics were typical of other ICD studies as well. The study also included a reasonable representation of minorities, including African Americans and Latinos.

While the mean age of the study is lower than cohorts from other ICD studies, you can see that there's a broad spectrum of ages represented. The S-ICD System was utilized in patients ranging from 18 to 85, and 60% of the patients were over 50 years of age.

A review of baseline characteristics of the IDE study cohort generally shows patients typical of an ICD indicated population. For example, the majority of patients enrolled in the study had comorbid conditions including congestive heart failure and hypertension. In addition, they had high rates of myocardial infarction, diabetes, and atrial fibrillation. All of these conditions are common to ICD recipients across the world.

Cardiac surgical history was also typical of an ICD indicated population. Of note, 43 patients in the S-ICD System IDE trial had prior transvenous ICD systems implanted. Heart failure was also prevalent in the study cohort. One hundred forty-six patients were Class II heart failure, and 55 patients were Class III.

The median ejection fraction was 31%. The mean of 36% was slightly higher than typical mean ejection fraction in ICD indicated patient populations. However, the distribution showed 70% of patients with an ejection fraction less than 35%.

The presence of several outliers was also noted. However, all patients enrolled met guideline indication for ICD implantation.

As seen in these pie charts, the study enrollment distribution of secondary and primary prevention patients is almost identical to the patient distribution present in the NCDR ICD Registry of nearly 500,000 patients.

Now, let's move to the effectiveness results. The effectiveness cohort consisted of 304 patients and was comprised of all patients in the safety cohort who completed the protocol-defined acute VF induction testing. One patient did not undergo acute VF conversion testing due to a persistent left ventricular thrombus. Sixteen patients were deemed non-evaluable as testing was stopped at physician discretion.

Therefore, under the protocol, these patients were excluded from the effectiveness analysis. The potential effect of excluding these patients from the effectiveness endpoint analysis cohort was examined via sensitivity analysis which we will describe shortly.

The primary IDE effectiveness endpoint for induced acute ventricular fibrillation conversion efficacy was designed to test the hypothesis that the performance criterion of 88% would be met with 95% confidence. The IDE study met this clinical endpoint. More specifically, the induced ventricular fibrillation conversion efficacy rate was 100% for the study. Additionally, the 95% lower bound was almost 99%.

Sensitivity analyses were used to assess the impact of the non-evaluable patients. The first analysis bracketed all non-evaluable patients who demonstrated at least one failed shock during their incomplete testing as a true failure. Eleven of the sixteen patients met this criterion resulting in the conversion rate of 96.5% with the lower bound at nearly 94%, well above the 88% OPC for this endpoint.

A worst-case sensitivity analysis was performed that imputed all non-evaluable patients and the one patient who was not tested as failures. This analysis resulted in the conversion rate of 94.7% with a lower bound of nearly 92%. Again, even with these worst-case assumptions, the lower 95% confidence interval for the conversion rate exceeded the 88% target established for the effectiveness endpoint.

Although not effectiveness endpoints, the FDA additionally asked Cameron Health to examine other prespecified analyses. I will walk through those now.

First, I'll examine the prespecified analysis for time to therapy for induced ventricular fibrillation. There were 838 events in the IDE study from both acute and chronic induction testing where VT or VF was induced and treated with 65 J. The mean time to therapy for the S-ICD System was 14.8 seconds. 88% of the tests yielded time to therapy results shorter than 18 seconds. More than 95% of events were treated in less than 21 seconds, a range consistent with transvenous systems. The few exceptions that were longer than 21 seconds were without clinical consequence.

Importantly, the performance of the S-ICD System during the IDE study is in line with recent literature supporting device programming that extends initial detection periods to eliminate inappropriate shocks and unnecessary appropriate shocks. There was no correlation between shock effectiveness and time to therapy in the IDE study.

The IDE study also includes results from a substudy of 77 patients who underwent chronic conversion testing after being implanted for at least 150 days. Seventy-four patients undergoing chronic conversion testing had evaluable results. Three patients in this substudy were not tested at 65 J in the opposite polarity as stated in the protocol and therefore were deemed non-evaluable.

Of the 74 patients who had evaluable results, 71 had success at 65 J. This resulted in a conversion rate of 95.9% at 65 J. Three failed at 65 J but were successfully converted at less than or equal to 80 J.

It is important to note that all 77 patients, including the 3 non-evaluable patients, were successfully converted at less than or equal to 80 J, which is the energy level delivered in an out-of-hospital setting.

These substudy results further support the continued effectiveness of the S-ICD System, which was the objective of the prespecified analysis.

As noted by FDA, the IDE study was not designed to collect a large number of spontaneous episodes. For this reason, Cameron Health worked with FDA to develop a prospective plan to collect episodes from additional sources. There were a total of 109 VT/VF spontaneous episodes in the IDE cohort. Non-IDE studies also provided another 52 VT/VF spontaneous episodes.

Finally, a commercial evaluation of spontaneous episodes provided another 51 VT/VF episodes. The effectiveness results from these additional resources all corroborate the performance noted in the IDE study. The episodes were characterized as discrete or as storms when three or more treated VT/VF episodes occurred within 24 hours. I'll now discuss those episodes.

There were 28 discrete spontaneous VT/VF episodes in 16 patients in the IDE study cohort over an average follow-up of 321 days. Nineteen of these episodes were monomorphic VT. The first shock efficacy for these spontaneous episodes was 95%. Remember, the S-ICD System delivers up to five shocks for each arrhythmia episode, and here we note that one monomorphic VT event spontaneously terminated after the first shock but prior to the second shock delivery.

The first shock efficacy for spontaneous polymorphic VT and VF episodes was 89%, which increased to 100% when using all five shocks for the episode. There were also four spontaneous VT/VF storm events in two patients in the IDE cohort. Within one storm event, there were 40 episodes with stored ECG data as well as 41 episodes without stored ECG data since the ECG storage capacity had been reached. Three storm events were associated with monomorphic VT. The conversion rate for this group was 100%. The majority of the spontaneous storm events were associated with polymorphic VT and VF episodes, and the conversion rate for these episodes was 100%, including the 41 episodes without stored ECG as they were largely witnessed by an IDE study investigator and successful conversion was reported.

Of note was one case in which the patient was externally converted not represented on this slide. This occurred following the final successful conversion of the S-ICD System of a storm event. Following the successful conversion, this patient who was already admitted to the emergency room again developed VF. The ER staff administered external defibrillation two seconds after charging commenced with the S-ICD System. The use of external defibrillation was unrelated to time to therapy for the S-ICD System, which recognized the external shock conversion and appropriately withheld additional therapy.

In conclusion, the data from the IDE study and non-IDE studies supports that the S-ICD System can reliably terminate ventricular tachyarrhythmias. The IDE study met its primary effectiveness endpoint. Chronic conversion testing results mirrored the acute endpoint data. Spontaneous episodes from the IDE study demonstrated the continued effectiveness of the S-ICD System, and these results are further supported by the additional data from the non-IDE cohort. The spontaneous episode conversion data from the commercial database provides further confirmation of the IDE study data.

Now I would like to discuss the safety results from the IDE study. Once again, here's a quick review of the cohort. 330 patients were enrolled in the IDE study. Nine patients withdrew from the study prior to implant, resulting in a safety cohort of 321 patients. The primary safety endpoint was a 180-day Type I complication-free rate. Type I complications are defined as those complications deemed to be directly related to the S-ICD System. The study measured the endpoint to test the hypothesis that the performance criterion of 79% would be met with 95% confidence. The IDE study met its primary safety endpoint at 99% with a lower bound of 97.9% as shown in this Kaplan-Meier curve.

In this chart, the yellow line shows the 180-day Type I complication-free rate of 99%. The solid white line indicates the 180-day performance criterion of 79%. The dashed vertical line in the graph demonstrates the 30-day incidence of Type I complications demonstrating a low perioperative complication rate of .6%.

As with the effectiveness endpoint, a sensitivity analysis and a worst-case analysis were conducted for the safety endpoint. There were 15 patients without Type I complications who did not reach the 180-day visit, including 7 patients who were not discharged with the S-ICD System after incomplete VF testing, 5 patients who had their S-ICD System explanted, and 3 who expired.

As will be seen in the following slide, these patients were conservatively included in the sensitivity analysis to demonstrate the robustness of the study endpoint. The results of these sensitivity analyses are shown on this Kaplan-Meier curve.

The protocol-defined sensitivity analysis looked at the Type I complication rate imputed at a rate equal to the endpoint complication rate. This resulted in a 98.7% complication-free rate, with the lower bound of 97.3%. The worst-case sensitivity analysis imputed all 15 patients as having Type I complications. This was calculated at 94.3% with a lower bound of 91.7%, still well above the primary endpoint performance criterion of 79% at 180 days.

An additional analysis was conducted to look at the safety performance of the S-ICD System beyond the 180-day endpoint. The 360-day complication-free rate was 97.1% with a lower bound of 94%, again well above the 180-day performance criterion of 79% for the primary safety endpoint.

We additionally examined the poolability of the safety data from the U.S. centers and outside the U.S. centers. The safety endpoint poolability analysis demonstrated no difference in 360-day complication-free rates between U.S. and outside U.S. centers.

Additionally, the poolability analysis showed no differences in the 360-day Type I complication-free rates between low, medium, and high implanting centers, indicating that the noted safety results were attained without requiring a high volume of experience with this system.

I would now like to take a deeper look at the safety data, and in particular the clinical events occurring in the IDE study.

A clinical event is any untoward medical occurrence in a patient independent of device-relatedness. All clinical events are then classified as complications which required invasive intervention and observations which did not.

Clinical events were also categorized based on their cause. Types I through III were those caused by the device, labeling, or procedure. When looking at the Type I through III clinical events, including all available follow-up data, one sees the following.

Among 37 patients in the IDE study, there were 43 events related to the device of which 10 were complications. There were four complications in four patients related to labeling in the study. Three were due to the investigator deviating from the specific implantation method in the user's manual resulting in suboptimal electrode placement or movement. One was due to an incompletely inserted electrode that was discovered after implant by x-ray. Proposed labeling and training materials will reduce the likelihood of similar clinical events reoccurring.

Among 84 patients, there were 24 complications and 82 observations which were not caused specifically by the device or labeling but would not have occurred in the absence of the S-ICD System implant procedure. Here we see a more conservative analysis examining the freedom from all device-, labeling-, and procedure-related complications. The 180-day complication-free rate shown by the yellow line was 92.1% and a lower bound of 88.9%. This was again above the performance criterion of 79% for the primary endpoint depicted in white. Also marked as a vertical dashed line on this graph is the 30-day postoperative point where you can see that the complication rate was 4.4%.

There were eight deaths in the IDE cohort. Six of the eight deaths were adjudicated as unrelated to the device or the procedure when the data was locked. The six deaths, unrelated to the device procedure, included two deaths for sepsis, secondary to (1) pancreatitis and (2) multi-system organ failure; two witnessed, nonsudden deaths for pump failure; one unwitnessed death secondary to pneumonia; and one unwitnessed death with restored ECG following successful termination of VT. Subsequent to the data lock, the CEC has adjudicated an additional death as unrelated to the device or procedure. This was a non-arrhythmic cardiac death. One death is still pending adjudication due to limited information as the death occurred overseas in Trinidad and little information is available despite all best efforts by Cameron Health.

Though the study was not designed to evaluate mortality, the annualized mortality rate in the IDE study was 3.7%. This rate is consistent with the rates listed on this slide found in most of the benchmark ICD studies performed over the last 20-plus years.

I would now like to walk through some of the specific device- or procedure-related complications one by one.

First, infection. In the IDE study, there were 18 suspected or confirmed infections in 18 patients. Four resulted in explants of the device, and 14 patients had incisional or superficial infections. Thirteen of the 14 were managed with antibiotics, and one was managed with a minor surgical revision to clean the sternal wound.

The data collection methods regarding infections were not prescriptive in the IDE study. The study accepted all reports of infections regardless of severity, ranging from postoperative incisional redness to positive cultures. However, collection of cultures and the use of antimicrobial therapy were left to the standard care practices at each institution. As a result, some reports of infection were likely superficial in nature.

This is supported by the data available on the 14 patients with reports of infections who remained implanted with the S-ICD System. In fact, 13 of these patients did not have invasive action and remained implanted free of a subsequent infection for an average of 430 days with the longest being 711 days. The 1.3% explantation rate noticed in the IDE study is similar to that reported in recent ICD IDE trials.

Interestingly, the timing of the infections were evaluated and noted that all four of the infections requiring explant occurred early in the study enrollment. There have been no explants due to infections in the last 214 IDE implants. Additionally, the timing of this change occurred around the time of its first investigators' meeting. At this meeting, experienced investigators shared their studywide learning; specifically, pointed discussions on patient prep and postop wound care prompted greater attention to infection prevention techniques by investigators.

Cameron Health used these lessons to develop and provide improved training materials for its field teams to educate new implanting physicians.

Again, while infections occurred within the IDE study, the large majority were successfully managed without explant or recurrence. No infection-related explants occurred in the last 214 of the patients implanted, supporting the effectiveness of the infection management communications in training.

Additionally, there were 43 patients in the IDE study who had prior transvenous ICD systems. 33 were explanted for infection. Of these 33 patients, there was only one report of a suspected infection with the S-ICD System, which was reported as resolved three days after implant.

Of important note, there were no reports on endocarditis, and there were no reports of bloodstream infections related to the system or procedure. These difficult-to-treat infections are associated with a high morbidity, and their absence is directly a result of the S-ICD System's novel subcutaneous placement of the electrode and device.

Now I will address inappropriate shocks. Thirty-eight patients experienced a shock due to a non-VT/VF event. Fifteen patients had SVTs and were above the program discrimination zone and in the shock only zone. This means the S-ICD System accurately detected the SVT rate, but due to the programming chosen by the physician, the S-ICD System delivered a shock. In some cases, use of the discrimination zone could have resulted in a different outcome.

In 24 patients, an inappropriate shock was delivered due to oversensing the patient's heart rate. The overall rate of inappropriate therapy with the S-ICD System is consistent with current transvenous ICD systems. As described in FDA's summary, approximately one-third of all shocks are inappropriate in a similarly indicated population with transvenous systems.

Of important note, no patients in the IDE study experienced a shock due to a discrimination error in the conditional shock zone or dual zone.

As I mentioned earlier, investigators in this IDE study communicated important lessons with one another, one of which was the potential benefit of dual zone programming and how it may lead to a reduction in inappropriate shocks. Following an investigators' meeting in January 2011, a higher usage of dual zone programming was noted. In fact, over the course of the study, we did find that dual zone programming was very effective in reducing inappropriate therapy. For oversensing, dual zone programming reduced the rate of inappropriate shocks by 54% over single zone programming.

For SVTs, the relative reduction in inappropriate shocks with dual zone programming was 74%. In dual zone patients, there was a much lower incidence of inappropriate treatment compared with single zone patients.

The third complication I'd like to specifically address now is discomfort. Twenty-one patients experienced discomfort in the IDE study. Seventeen patients did not require invasive treatment. Four were managed with system revisions. The four system revisions served to revise a protruding electrode suture, a torn pulse generator suture, a pocket revision related to a hematoma, and one instance where the pulse generator was repositioned due to an interaction with the patient's bra strap.

Reports of discomfort in 12 patients were related to the surgical procedure, and no reports of discomfort were so severe as to require explant over the follow-up period.

In summary, the data demonstrate a reasonable assurance of the safety of the S-ICD System. The primary safety endpoint was met. One year data provides further support of continued safety. Significant clinical complications were infrequent and very manageable. The rate of inappropriate shocks is comparable to transvenous systems. There were no infections requiring explant with the last 214 implanted patients, and no explants were required due to discomfort.

Again, although the IDE study was not a mortality study, its rates were also comparable to traditionally accepted ICD studies, and the lessons learned during the IDE study will be beneficial and have a broader utilization of the S-ICD System.

Overall, the S-ICD System IDE study met its endpoints.

First, the study data demonstrated effectiveness of the S-ICD System. In addition to the primary endpoint being met, chronic conversion results were consistent with the acute VF conversion data. Spontaneous episode results further support the chronic effectiveness of the S-ICD System.

Second, the study data demonstrated the safety of the S-ICD System. The primary safety endpoint was met, and the additional analyses reviewed today provide further support for the safety of the system. Also of importance, significant complications and observations were infrequent and manageable.

In summary, the results of the IDE study point to a functional and safe device.

I'll now ask Alan Marcovecchio to address Cameron Health's labeling and training program as well as its post-approval plan.

MR. MARCOVECCHIO: Thank you, Dr. Burke. I'm Alan Marcovecchio, Director of Clinical and Regulatory Affairs at Cameron Health.

Developing a lifesaving device that conforms to good laboratory practices and is well supported by clinical data is only part of Cameron Health's mission. We are committed to working with the FDA to ensure labeling and training are available for the safe and correct use of the S-ICD System in appropriate patients.

We have also developed a post-approval study plan that we will design interactively with the FDA to demonstrate the continued safety of the system in a commercial setting.

Clear, informative, and detailed labeling is, of course, essential to the correct use of the S-ICD System, and Cameron Health will collaborate with the FDA on final labeling that satisfies these objectives.

The labeling we are proposing is comprehensive and has been adjusted to include information learned during the IDE study. Examples of labeling clarifications involve updating the list of potential adverse events, clarifying the screening tool instructions, and describing how the use of dual zone programming can reduce inappropriate shocks.

Information has also been added to the user's manual to clarify the assumptions for longevity estimates and to clearly explain that additional charging and shocks will shorten battery longevity. As described by Dr. Gold earlier, at the time of implantation, the S-ICD System has the capacity to delivery more than 100 defibrillation shocks. An estimated longevity of 5.4 years assumes 21 full energy charges over the life of the device. This longevity estimate also includes typical assumptions that the system will be interrogated by the programmer four times per year and that it will charge to full energy just over three times per year. The assumption of three charges per year is also supported by the IDE study data. Additionally, longevity estimates have been confirmed by analysis and device rundown testing, and the labeling more conservatively presents a nominal longevity of five years. As with all ICDs, shock capacity and longevity are a function of one another. An increased need for therapy such as treatment for VT storms impacts device longevity.

Cameron Health designed a training program to ensure implanting physicians and their support teams receive consistent, high quality training before using the S-ICD System. Training will be provided to physicians currently implanting ICDs who are familiar with defibrillation testing. Training materials will incorporate the lessons learned from the IDE study, which were discussed today. Field representatives will be certified to ensure they are sufficiently knowledgeable about the device functionality and implant procedure before training physicians. Physicians will receive didactic training from certified representatives, and that training will cover system functionality, implant and follow-up procedures as well.

To further supplement training, educational tools, such as the implant video seen today and system emulators, will be available. Lastly, Cameron Health will facilitate proctorships when requested.

Again, Cameron Health will work with the FDA to develop this training program.

In addition, Cameron Health has been working actively with FDA to develop a post-approval study for the S-ICD System. An initial post-approval study was presented to FDA, and FDA provided Cameron Health with feedback on that plan. In response, Cameron Health revised the post-approval study which is now included in the Panel materials.

The study is intended to assess the long-term safety and effectiveness of the S-ICD System in a representative population of patients in a commercial setting. The study is similar to previous post-approval studies approved by the FDA and is a prospective, multicenter, non-randomized study which will be conducted exclusively in the United States at approximately 50 centers.

The design includes a 60-month follow-up period, which is consistent with FDA's standard for examining the long-term safety of ICD systems.

Logistically, Cameron Health is proposing to conduct the study in collaboration with the ACC/NCDR ICD Registry. The ICD Registry is a benchmark for ICD implant data and will provide a means for independent third-party management of post-approval study data.

The proposed study will include patients currently implanted in the IDE study who already have significant follow-up time. The study targets an additional prospectively enrolled cohort from approximately 50 centers. These centers will be NCDR premier centers comprising a range of academic, private practice, and geographically diverse implanting centers. The study will attempt to include all U.S. patients from the IDE cohort, and approximately 700 new patients will be enrolled in a new cohort for a total of approximately 1,000 patients. This considers an expected attrition of 20%.

The exact sample size will be based on the final study design to be agreed upon with FDA.

The study endpoint proposes to evaluate the 36-month system and procedure-related complication-free rate. This rate will be compared to an objective performance criterion derived from the IDE clinical study data in collaboration with FDA. Endpoint events will include all device- and procedure-related clinical events requiring invasive action. This definition is similar to the analyses conducted in the IDE study that looked at freedom from any complications related to the device or procedure.

Thirty-six months will provide important long-term data on the post-approval study cohort, and in addition, substantial data through 60 months from the IDE cohort will be available at that time. Additional prespecified analyses for effectiveness and safety are shown on this slide. To confirm effectiveness, mortality estimates will be reported, and spontaneous episodes will also be reviewed. Subgroup analyses evaluating any potential gender differences will also be reported.

Cameron Health's post-approval study is a robust plan and will provide data that will confirm the continued effectiveness and safety of the S-ICD System.

While the NCDR Registry will capture the majority of the targeted data, spontaneous episodes and mortality data are not part of the ICD Registry, and a supplementary mechanism will provide the means to collect those effectiveness-related data. Spontaneous episodes and deaths will be independently adjudicated, and recognizing that the Social Security death master file will no longer be available to researchers, Cameron Health is working with ACC to identify an alternative means to gather these data.

To minimize the potential for missing data, Cameron Health also plans to implement active monitoring for the NCDR and supplementary mechanism. This active monitoring will involve periodic reviews of patient medical records to ensure all reportable events have been entered.

Now I would like to invite Dr. Gold to the podium to offer some closing remarks.

DR. GOLD: Thank you, and my thanks to this Panel for its time and attention during this morning's discussion regarding Cameron Health's

S-ICD System. You've heard today how this system is an evolution in the post-ICD therapy and the results of a decade-long development program.

In closing, I would like to discuss how the benefits of the S-ICD System far outweigh the risks in the indicated population. The potential risks are shown on this slide. Inappropriate shocks were noted in the IDE cohort. However, as indicated by the FDA in the Panel pack, the rate of inappropriate shocks is comparable to a similarly indicated population with transvenous systems. What was also demonstrated was how the rate of inappropriate shocks could be decreased through non-invasive reprogramming. As discussed during Dr. Burke's presentation, the use of dual zone programming led to a substantial reduction in inappropriate shocks, and Mr. Marcovecchio explained how the company plans to incorporate the lessons into its training program.

Infection was also noted in the IDE study. However, infection rates were greatly reduced following the investigator meeting at which physicians were educated about the lessons learned from the study. More importantly, those same lessons learned will be included in the S-ICD System training program. Of additional importance, infections were easier to manage than traditional transvenous ICD infections, and due to the subcutaneous placement of the S-ICD System electrode, there were no reports of endocarditis or bloodstream infections in this study.

I would like to discuss the matter of battery longevity. At the time of implant, the system can deliver over 100 shocks. However, the 5.4 year lifespan is based upon more typical assumptions. It is important to remember, like all devices, battery longevity is impacted by the number of shocks delivered.

Time to therapy also may initially appear longer than some commercially available devices. However, again, I would like to remind you that recent ICD studies indicate that allowing for an extended discrimination period results in spontaneous termination of many arrhythmias, both supraventricular and ventricular, reducing the requirement for therapy. In addition, no clinical correlation could be made in the IDE study between time to therapy and any clinical consequences.

As you've heard today, the S-ICD System is an advance in implantable defibrillator technology. Since the S-ICD System is implanted entirely subcutaneously, this unique system addresses the numerous implantation and explantation risks that hinder well-established therapy for transvenous ICDs. Specifically, the S-ICD System eliminates a need for leads to be replaced intravascularly. Furthermore, the system can be implanted using anatomical landmarks, eliminating the risks of procedural complications associated with medical imaging.

Finally and significantly, as Dr. Burke described, the IDE study endpoints were met, and these endpoints were robustly supported by additional prespecified analyses and supplemental data from outside the IDE study.

For all the reasons outlined today, I can say that the benefits of the S-ICD System outweigh its risks and would offer tremendous advantages of current treatment options for patients. The totality of evidence establishes a reasonable assurance of the effectiveness and safety of the S-ICD System for the intended population when used in accordance with the labeling.

We thank you for the opportunity to discuss the S-ICD System and its potential for treating patients at risk for life-threatening ventricular arrhythmias.

With that, I invite Mr. Marcovecchio to return to the podium.

MR. MARCOVECCHIO: Thank you, Dr. Gold. I, too, offer my many thanks for your attention this morning, and at this time, we would welcome any questions that the Panel may have.

DR. LASKEY: I'd like to thank Dr. Gold and colleagues for a great cogent presentation. We have about a half an hour that we can have some Panel querying of the Sponsor at this point, keeping in mind that we'll have additional opportunities this afternoon. However, if we can frontload the questions, that would be preferable.

So Panel members in turn. Yeah, Dr. Dehmer.

DR. DEHMER: If you could put up slide 46 again. I have a question about your slide 46. So looking at the flowchart, you get down to the last group that's excluded, and you have exits after hospital discharge, n=20, and on the next slide, 47, you provide a fairly detailed explanation of those 20. Now, go back a slide. Explain to me what happened to the seven that were not discharged with the system because it looks like it got put in and then was taken out. Can you explain that further?

MR. MARCOVECCHIO: I'll invite Dr. Burke to address that question.

DR. BURKE: So in that graph, you can see that seven patients were explanted prior to discharge from the hospital, in which case they did not meet the effectiveness endpoint, and so from a consequence of not being able to be defibrillated with the system, the investigator felt that it was not in their best interest clinically to remain with the device.

Now, there were 17 patients that had that clinical circumstance, of which 10 kept the device in place and were included in the safety cohort, but as you can see from our future slides in this particular presentation, those 10 were included in the sensitivity analyses.

DR. DEHMER: Thank you.

DR. LASKEY: Dr. Kelly.

DR. KELLY: I had a question about the patients shocked for oversensing T waves. I noticed in your cohort there were a fair number of patients with Long QT and Brugada Syndrome, and I wondered if the oversensing T wave patients tended to be those that might have dynamic T wave abnormalities.

MR. MARCOVECCHIO: I'm going to invite Dr. Gold to address your question regarding inappropriate shocks and the potential relation to those particular patients.

DR. GOLD: Thank you. We did not see any specific clinical characteristics that were associated with a high incidence of the oversensing. In most instances of oversensing, we were able to program around that or the investigators could program around that by changing the vectors. One of the unique and nice aspects of the Cameron Health system was, in fact, that you have three different vectors, and when oversensing was seen, frequently going to another vector would increase the R to T wave ratio and prevent that, but it did not cluster with, as I think you appropriately point out, conditions that we'd be worried about, T wave oversensing, such as the Long QT or Brugada patients, although that was a relatively small group of patients in the study.

DR. KELLY: Okay. Thanks. Can I ask you one more question about the patients with discomfort? I mean I heard you had some very small patients, but the BMI was 30, so these were a pretty large group, and there weren't a lot of women. Did the women or the smaller people tend to have more discomfort, or do you know that?

DR. GOLD: We do know that. You've got a perceptive question there. There was no relationship between BMI and discomfort ratios per se, but women did have more discomfort, and if I might call Dr. Russo up to the podium because she really was the one who spent the most time analyzing the discomfort issue.

DR. RUSSO: Hi. Andrea Russo. I'm Director of Electrophysiology at Cooper University Hospital in Camden, New Jersey, a Professor of Medicine at the system there also. I am a paid consultant and also am being reimbursed for my time here today and travel.

We did have a good number of women enrolled in the trial, and it looks like there was a higher report or incidence of discomfort in women than in men overall in the trial, the study. The specific descriptions of why that might be, as you can imagine, women dress differently. We have different clothes that we wear, and particularly complaints of soreness over the area of where the bra is located is part of it, and also the actual incision in the inframammary area. I can put that slide up there. I think I can. There I can. You can see the incision is, you know, in close proximity to a relatively sensitive area. I would imagine that, you know, perhaps that was a big component of why they had more soreness than men did in that particular region, the generator, and clearly that's something you can, you know, you could fix, move the incision to a different place and still have the pulse generator in the same location. So I think it was more related to the incision, the inframammary area, as well as where the generator sits.

DR. KELLY: Okay. Thank you.

DR. LASKEY: Dr. Somberg.

DR. SOMBERG: Well, I'd like to congratulate the Sponsor for an excellent presentation and excellent planning of the development program. It's really a nice example of what others should copy.

I have a question about -- two questions really. One is to do with the device longevity and the potential storms. If the battery depletion is accelerated, for instance, like an incessant VF or something like that, is there a warning that comes? I remember hearing there was some sort of audio signal. Is that related to that?

MR. MARCOVECCHIO: The device is designed with similar mechanisms that current transvenous systems have. The programmer screen itself gives the clinician an indication that the battery is approaching the elective replacement indicator, and once that point is reached, similar again to other devices, an audible tone is, in fact, emitted from the device for the patient to recognize as another precaution to contact their physician.

DR. SOMBERG: Okay. I thought so, and you're reminding me. So with that said, should there be a patient training manual as well for the device to deal with it, and, you know, just parenthetically, I mean people do have different garments, et cetera, gender differences, et cetera. There might be recommendations in how to deal with this sort of thing. Just a suggestion for you guys.

Also in the post-approval study, you talk about a premier implantation group. Is that going to be -- and you mentioned academic centers, et cetera. Are you going to make extra effort to try to bring in, you know, one of the purposes of a post-approval study is real world experience. So if you just use your premier people who have had experience already, you're going to get a non-generalizable observation. So are you going to try to get non-premier people involved?

MR. MARCOVECCHIO: Actually, I'd like to invite Dr. Kremers to provide a clarification on that important point you mention.

DR. KREMERS: Good morning. My name is Mark Kremers. I'm a clinical electrophysiologist from Charlotte. I'm a paid consultant to Cameron Health. I was also an IDE investigator on the SID study. I am the NCDR ICD Registry Steering Committee Chairman.

Relative to a premier center, a premier center is a NCDR designation that specifies that the centers have self-selected themselves to enroll all patients in the NCDR ICD Registry study. It is not a reference to quality and, in fact, 80% of the centers enrolling patients are premier, and they enroll 90% of the implants in the United States. Thus, there will be a wide representation of large centers, small centers, and lots of experience differences.

DR. SOMBERG: I appreciate that, but wouldn't it be that the people are differentiating themselves. Those who enroll everybody will be a little bit different than those who selective enroll only what they think they want to enroll? So there might be a bias there. Just consider it. There might be a bias there introduced.

DR. KREMERS: Accepting there could be a bias, I would think that it is, in fact, a favorable bias as these centers have committed themselves to exceeding what is required of them, enrolling all patients, not just Medicare and primary prevention, number one.

Number two, the principal reason for confining the post-approval study to premier centers is that premier centers track not only all patients, but they also track leads and therefore lead-related complications. Lead-related surgeries will be part of the NCDR database with premier centers and would not be with non-premier centers.

DR. SOMBERG: Thank you.

DR. ZUCKERMAN: Can you clarify one other comment since we're on this issue? At a premier center, given the technique that's been shown, an interventional cardiologist, non-electrophysiologist could be the implanter for this device?

DR. KREMERS: Non-electrophysiologists do implant ICDs. In the registry, they are a distinct minority constituting about 2%. Cameron Health is committed to keeping this device at least initially in the hands of implanting electrophysiologists.

DR. ZUCKERMAN: Is that in the post-approval study or anywhere in Cameron Health's Panel pack?

DR. KREMERS: I'm going to defer to Mr. Marcovecchio.

MR. MARCOVECCHIO: I cannot recall if that specific point is enumerated in the Panel pack, but I can say that our intention as the Sponsor is to direct the use of this device to those physicians who are currently trained and experienced with defibrillation testing, which clearly is an important part of using the devices, and we're committed to working with FDA to figure out the best way to add language in the appropriate places to make that happen.

DR. LASKEY: Just to say on this point, it may be worthwhile discussing it a bit more this morning rather than this afternoon. So on this theme, other than perhaps a modification of the objectionable terminology, Dr. Somberg, from premier to something less elite, but are there other Panel members who want to weigh in on the user, the appropriate user.
Dr. Somberg.

DR. SOMBERG: I'm just concerned that what I meant as a bias is, you know, I understand the people who report are excellence and they're compulsive, and they're very good for study, but one of the purposes of a postmarketing study is to see what happens, if you will, the "stragglers" and the people who have low volume experience and if there's something that's needed to help them. So I just wanted to advise you that that is a consideration.

I understand where Dr. Zuckerman is coming from, and many of my colleagues in electrophysiology, they have certain expertise, but there are national priorities and there's a shortage of electrophysiologists, and there's, you know, need for more defibrillators as these studies generalize. So there's going to be more people implanting them. Interventional cardiologists and cardiothoracic surgeons I can see in this area. So some thought should be, in my opinion, given including those in a follow-up to see if there are distinct problems of, you know, I can see one group maybe even doing the implantation better and the other group doing the follow-up and the electrophysiology far better. So there may be needed differential emphases.

DR. KELLY: As far as the implanting physician, I think we've kind of been there, done that with the data from the last NCDR study looking at non-evidence-based implants and non-electrophysiologists. There was a fairly clear difference between electrophysiologists who have the lowest and then cardiologists and then cardiac surgeons and others that there were just a couple of. So at least I think if we're going to have non-electrophysiologists implanting them, the criteria for implant have to be pretty clear.

DR. LASKEY: Perhaps -- okay. Rick, you first.

DR. LANGE: A couple of things. One is I'm wondering if things that could change impedance, change the efficacy, and that things like COPD and/or the patient's height, less than the weight, but that is the height. So this afternoon if you guys can present any data that you have regarding that.

MR. MARCOVECCHIO: Just to confirm, your question is regarding COPD and other things that might affect impedance, and what was the other point please?

DR. LANGE: And the patient's height. In other words, you've got a fixed lead size. So someone that's 6'6 versus someone that's 5'.

MR. MARCOVECCHIO: Sure.

DR. LANGE: Okay. And then you had mentioned that one of the things you all learned was that inadequate labeling or situations where labeling wasn't followed resulted in some of the events or observations that were noted, and that's changed the labeling. And I could find in the labeling very specific instructions on lead connection and using a non-absorbable suture, which was great, and I'm wondering if there's information in the user's manual that talks about either EKG screening, to clarify that, or the preparation. You talked about changing the prep, and then finally whether there's information on dual chamber zone pacing in the user's manual as well. So if you guys could share that this afternoon, that would be great.

DR. LASKEY: Okay. Ralph.

DR. BRINDIS: I have two questions. A terrific presentation. How many -- were there any patients in the study ended up requiring need for a permanent bradycardia pacing, that is permanent pacemaker placement, just sort of an interest for me in terms of, for a clinician going forward, and again I appreciate that some of the patient population here is younger than the patient population that we have in the NCDR.

And the second question is related sort of to discomfort. Does twiddling occur at all with patients with the subcutaneous leads and particularly subcutaneous lead concept, particularly in patients with low subcutaneous fat?

MR. MARCOVECCHIO: I can answer the question right now with regard to bradycardia pacing. There were no patients explanted due to a need for bradycardia pacing.

With regard to the twiddling, I would have to gather that information, and I can present what we have after the break.

DR. LASKEY: Dr. Dehmer.

DR. DEHMER: This is a bit of a follow-up to the question from Dr. Lange, and maybe you can provide some insight to us. I probably should clarify that I'm an interventional cardiologist. So if this is not exactly correct, maybe Dr. Kelly next to me, who is an electrophysiologist, can poke me and say I'm in the wrong direction, but do you have any comments, at least my understanding is when patients that have a traditional transvenous defibrillator system start having too frequent shocks that become very troublesome to them, that frequently they're started on some antiarrhythmic drug to further suppress the likelihood that they're going to have these unpleasant shocks, and that the antiarrhythmic drugs can change your defibrillation threshold. Do you have any data on what has happened in any of your patients, that if they get started on an antiarrhythmic drug, for example, like amiodarone, how that affects your device performance.

MR. MARCOVECCHIO: I'd like to invite Dr. Gold to address that question please.

DR. GOLD: Certainly VT storm is a challenging problem for all of us when we do patients, not unique to subcutaneous ICDs. We see them with all defibrillator systems. There are a number of strategies of how to treat VT storm. I'm not sure any of us feel comfortable that we know the right strategy to use. Beta blockers surprisingly have been shown to be as effective, if not more effective, than many antiarrhythmic drugs, but we frequently use antiarrhythmic drug therapy. VT ablation as a therapy for that. Blood pump placement's been used, intra-balloon pump. General anesthesia has been used, and so on and so forth. So we don't, you know, have one strategy that fits all.

With regards to antiarrhythmic drug therapy, there was no examples in the VT storm that the device was very effective. Most of those patients at some point, I don't have the precise number at hand, most of those patients at some point were given antiarrhythmic drugs, and we don't have any evidence of device, of shock failure because of the antiarrhythmic drugs.

I should point out again of the antiarrhythmic drugs we use, drugs such as dofetilide and sotalol are drugs which, if anything, reduce defibrillation thresholds of transvenous leads. Amiodarone, which you already show and already mentioned, is a drug that various reports that it may increase defibrillation thresholds. We saw no signal for that, but there wasn't any comprehensive or systematic retesting of defibrillation efficacy on amiodarone within the study.

DR. LASKEY: Dr. Milan.

DR. MILAN: I have some questions about the substudy that have studied the efficacy for conversion of induced VF at greater than 150 days. How are the patients selected to be in that substudy?

MR. MARCOVECCHIO: I would invite Dr. Burke to respond to that question.

DR. BURKE: The substudy was actually an enrollment that took place at specific centers. Not all centers were actually agreeing to enroll in that particular study, and that's why it was, you know, somewhat smaller than the overall study cohort. Say in our center, we offered at 150 days that particular substudy to every single patient, whereas some study sites did not feel that it was appropriate because of data that's out there about long-term DFT testing's effectiveness and clinical applicability not being quite there. So in that circumstance, that's why there's 77 patients enrolled in that particular substudy.

DR. MILAN: So there was some self-selection by the patients as well?

DR. BURKE: It wasn't necessarily, at least in most the -- in the 77 patients that were selected, it was really the patients that decided to move forward because they felt strongly that they wanted the device approved.

DR. MILAN: So there were six patients that had some sort of issue at the follow-up. Three were non-evaluable because they didn't complete the full battery of ICD testing, and there were three frank failures. Were there any indications from the implant testing that those patients were going to have problems?

DR. BURKE: No, and you know, it's sort of a difficult comment to say; it's just frank failures. You know, in actuality, they were all successes at 80 J, and what we took in that particular substudy was attack that. We were going to try and keep it as real-time as it were, and it was a one-shock efficacy study. It was very different than the primary effectiveness testing. And so when we're looking at the implant conversion testing, we required two consecutive conversions from four attempts within a given polarity.

In the chronic conversion substudy, we required one conversion from one attempt within a given polarity, and the three that were not evaluable did not go to the opposite polarity, and they just allowed them to go to 80 J, and they said that's, you know, we're good. We feel comfortable with that, just like we would, you know, with the transvenous

DFT testing chronically. We'd go to that, and then we'd go to the max output and be happy.

DR. MILAN: So let me differ with you about that last statement that you said because I agree that we do a single test in follow-up, but the goal of that is to establish safety margin for defibrillation, and it sounds like at least for those three patients, there was no safety margin. They were only converted at the max output of the device for the single test that was performed. Is that right?

DR. BURKE: Well, they had all been previously converted with a large safety margin actually. So we feel like from a DFT testing standpoint and looking at the probabilistic curve, that the safety margin was established at implant, and then with the substudy, we felt confident that with the probabilistic curve that any one given shock can be successful or fail, that the comfort level was right there if they successfully converted at the clinically useful 80 J.

DR. MILAN: If I could continue along this line then. Around the time -- actually the historical context was useful that Dr. Gold presented -- around the time that we were converting from abdominal devices with epicardial patches to transvenous leads sometimes with subcutaneous patches, there were reports that DFTs would sometimes rise, and there was a lot of work done in the '90s to investigate what might be the causes of rising DFTs, and it looked like putting in active can prepectoral devices with dual coil leads and biphasic waveforms took care of that problem.

But with your data here, with no hints in these six patients that there were problems at implant, but captured only at max output, I wonder if you have any data that would dispel any concerns that these patients might actually have rising defibrillation thresholds over time.

DR. BURKE: The substudy and subsequent chronic conversion testing study was not designed to answer that particular question.

DR. MILAN: Based on the -- well, there's really almost 8% of the patients who were either non-evaluable or only captured at the max output. Do you think everybody should undergo subacute testing or chronic testing of their device? And what is the recommendation for a patient who is non-evaluable or can only be converted at the max energy? Should they -- the reason I ask is because transvenous systems are very good at getting 10 J safety margins which is really probably the clinical standard of care even today despite some controversy about primary prevention devices. And so leaving a patient who could only be cardioverted at the max output or was only demonstrated to be cardio converted at the max output of their device, when you know you have an alternative that is extremely safe, I'm just wondering, you know, where do we cross the line. You know, our job as clinical electrophysiologists is to guarantee the safety of our patients, and I'm just curious about what we do with a non-evaluable patient and follow-up.

DR. BURKE: Let me just comment that, in the substudy, we were still above the OPC for success effectiveness. So I think I feel comfortable with this device, that it does successfully convert at 65 J with the safety margin.

The concepts, further of what you were discussing related to transvenous, I'm not sure that it's a defibrillation methodology. It's defibrillation in general. With biphasic waveforms, things are very stable. But let me have Dr. Gold come up and reiterate some of the points and try to answer some of your questions as well.

DR. GOLD: I think you make an interesting argument there. I should point out that what was done at implant with this was not to use the traditional 10 J safety margin, but was to use a 15 J safety margin. So there was a greater safety margin than one might use clinically. One of the, if you might say, glitches in the system is that at follow-up we didn't test if there was a 10 J safety margin. So we were testing if there was 15 J safety margin. If one simply does probabilistic modeling of defibrillation at a 15 J safety margin, if the success rate is, you know, on the order of 95% or so, at a 10 J safety margin, one would expect a success rate on the order of about 98 or 99%, which is precisely what you'd want for a transvenous system.

We had done a study, called the LESS study many years ago, that you may be familiar with, where we gave many more shocks than this to patients trying to really precisely define that sigmoidal defibrillation efficacy curve, suggesting, and it was part of the reason why we did the power calculations assuming a 93% success at 15 J, we would be very good.

So we certainly, I think with the numbers we got at follow-up, would feel comfortable that we were on the asymptotic limb of the defibrillation efficacy curve, no difference. Because of the difference in the way we tested at implant the protocols, we really couldn't assess or ascertain any measurable difference in defibrillation efficacy, and probably the most reassuring to me was we spent a lot of time, I probably spend more than most of you, talking about defibrillation efficacy and safety margins and all of this, but it's the real world we care about, and the device performed impeccably in terms of spontaneous arrhythmia. So we saw no signal that we were failing to defibrillate patients, and as much as we may test in the lab, that's what we really care about and, you know, it was near perfect for that. So all of that was reassuring to me.

DR. LANGE: Again, I'm not an electrophysiologist, but I want to follow up with David because -- just to understand the issue. That is, these were all individuals that were terminable at 65 J at the initial testing, and then at follow-up three were not, but were terminable at 80 J. But what we don't know is what that safety margin is in those patients. We don't know whether it's 15. Well, we know it's not 15. We don't know whether it's 14 or 2. So the real question, I guess, to follow up on David is what to do with those patients. In other words, nowhere -- there's no way to assess with the current program what that safety margin is.

DR. GOLD: Yes. So, again, just as a reminder, the differences because the two protocols which I have up here on the screen, so at implant, it was two consecutive conversions out of four attempts. So you could miss your first shock, which happened in a few patients, and then your second and third shock were successful and you're successful. At the chronic conversion, it was just that one shock. So if you missed that first shock, you'd be called a failure even if you might have gotten that second and third shock. So it may be no different in that situation. So we don't have that data, but we don't have -- and we need the Cameron Health people to remind me of the exact programming values that you can use during testing of this 65 versus 80. Is there an in between number?

UNIDENTIFIED SPEAKER: No.

DR. GOLD: So it's just the 65 versus 80. So the device doesn't have a setting to allow you to more precisely quantify that, but again to remind people, this a probabilistic phenomenon that was seen over and over again in testing. Threshold is a misnomer. It's probabilistic. So even if we got someone at 65, missed them and got them at 70, the next time you can come around and get them at 65 and miss them at 70, and you're scratching your head and saying what's going on, and that's just the nature of probability.

DR. LASKEY: And I think that's a very articulate answer, Dr. Gold. It might help to remind the Panel how few patients we are talking about. These are valid points that come up, and certainly going forward, there are going to be more of these if you've observed this as many times as you have, but just remind us how many of these patients we're talking about. Three.

DR. GOLD: These were three patients who did not succeed at 65 J and were successful at 80 J out of the cohort.

DR. LASKEY: Okay. We have five minutes left to this period. So, Dr. Dehmer first, and then Dr. Somberg, and I have a closing comment.

DR. DEHMER: So I'm going to go back to those seven patients that had the device put in. It was tested. Apparently it just failed. It didn't work, right? So you took the device out?

MR. MARCOVECCHIO: Actually the testing, the full protocol testing --

DR. DEHMER: Right.

MR. MARCOVECCHIO: -- was not completed. So we view them as non-evaluable.

DR. DEHMER: Okay. I guess I misunderstood then what you said earlier. You have the 20 patients where you explained why the device came out during the follow-up, but there were 7 patients where the device went in and then they never left the hospital with it. Isn't that right?

MR. MARCOVECCHIO: These are patients where the initial testing was performed.

DR. DEHMER: Right.

MR. MARCOVECCHIO: They did complete not the testing, but the implanting physician did not feel comfortable enough that it would be effective in the patient, and they took the device out before the patient left.

DR. DEHMER: So did they get a traditional transvenous defibrillator unit at that point or --

MR. MARCOVECCHIO: I don't know the answer to that question.

DR. DEHMER: Okay.

DR. LASKEY: Dr. Karasik.

DR. KARASIK: So I have a question on the other end. Could you or someone discuss the screening tool used prior to implant and whether or not there are patients who don't need screening based on their ECG signal due to the presence of bundle branch or something to that effect?

And then to follow that question, were there any episodes of undersensing? We've heard a lot about oversensing, but did you see any undersensing? Was that a contributory factor to the length of charge times and things like that?

MR. MARCOVECCHIO: I'll invite Dr. Burke to address both of those points.

DR. BURKE: Reliable sensing and detection, why don't I start there, and then I'll talk about the screening tool. So acute and chronic VT/VF detection sensitivity for the 898 inductions had successful detections in 99.8%. There were some points where you look at the time to therapy, and they're on the outer limits, and so there was some points in VF where you would have some drop off like you normally see in a transvenous system, and the system then picks up and recalibrates and redetermines that this is ventricular fibrillation. So from a sensing standpoint, in the IDE study, we have not noticed any type of undersensing for a prolonged period of time that would make us have any pause. The S-ICD System can reliably sense and detect ventricular tachyarrhythmias.

From the sensing, to get to the point of the screening tool, that was a key feature in getting to that successful sensitivity, and so when we look at the screening tool itself, in the IDE study, with the initial screening tool, everybody that was screened with the tool in positional changes met criterion for implant. Nobody was excluded because of the screening tool in the IDE study.

However, there were two patients that were explanted due to sensitivity issues for oversensing and repeated oversensing despite the tool, and these two people required explant for the S-ICD System due to oversensing. And consequent to that, we went back and looked retrospectively to analyze a change in the screening tool, and with the revised screening tool instructions, you know, taking into account our wave amplitude to the T wave ratio, we were able to come up with a more successful and would have excluded those two patients and would have also excluded seven other patients. And so the updated instructions, which will be in this next labeling and post-approval study, will lead to additional fallout of the seven patients who account for about 2.2% more of the population and will hopefully decrease the oversensing issue.

DR. LASKEY: Dr. Naftel.

DR. NAFTEL: So, as I understand, the battery life is 5.4 years. So I'm real interested in what happens at that point, and then we'll have the discussion this afternoon I'm sure on the post-approval study, but I'm thinking it sounds like you're going to stop follow-up at 60 months, right before the end of the battery life, right before a real important time. So this afternoon, I'll suggest fewer patients but for a longer period of time. So I'll suggest that then, but right now my question is, what happens when the battery is finished?

MR. MARCOVECCHIO: Sure. I think your question is actually applicable not only to our device but also to transvenous devices. I'd like to have Dr. Gold come up and explain how patients are managed as the battery approaches the end of life.

DR. GOLD: Thank you. This is very similar to what we do with transvenous lead systems. So the battery reaches what's called ERI, which is elective replacement indicator. So the battery is not dead at that point. We've already talked hopefully ad nauseam about the 5.4 years that we expect out of this device, but at the time that it trips to ERI, there is 6 full energy shocks and several months left in the device, which is again very comparable to ICD system. So it starts to beep or their monitor, whatever, and then you electively plan to replace the pulse generator, you know, presumably with a normally placing lead so that this would be an outpatient procedure just like we do today. So this is a very standard procedure that we do with all implantable devices.

DR. LASKEY: Okay. Dr. Lange, take us and then Mr. Dubbs, and then we'll take a break. Rick.

DR. LANGE: Just some questions that you guys can answer on the break, not right now, but one is there were two patients oversensing due to use of electrical equipment. So if you could tell us whether those are arc welders or hair blowers would be helpful.

Tell us what you know about their exposure to MRI with this unit, and then finally, in the patient information, you encouraged the patients to keep their phone 6" from the device. And so any information you can give us regarding that, and what you know about that, would be helpful. Thank you.

DR. LASKEY: Mr. Dubbs.

MR. DUBBS: Can you explain the under-representation of women and what you intend to do in a postmarketing study to get more women to participate in terms of affirmative action?

MR. MARCOVECCHIO: Sure. With regard to the representation of women in the study, I'd like to invite Dr. Russo back to the podium to address that point.

DR. RUSSO: Great. Thanks. So, in general, this study, women are not under-represented. In fact, we have more women enrolled in this study than in multiple randomized clinical trials that have been done previously. It's just that, in fact, at our center, I can tell you, I enrolled 40% of my patients were women, and I think it's a great device for women and it's a great option. So it's the general -- there is some controversy and actually, you know, one of my areas of interest is looking at, you know, gender differences and usage of ICDs, and I think part of it is just that women less often have ischemic heart disease, and that's where, you know, as you get older and you require devices, you know, the denominator are more men than women, but I think compared to previous clinical trials, you know, clearly and to the ICD Registry, which is the real life, this is where we're at, and so I think it's actually well represented women.

DR. ZUCKERMAN: Okay. Dr. Russo, I don't want to quibble about well represented, et cetera. I think you could help us if you perhaps give us some tips about how did you get 40% at your site as opposed to the overall average of about 25% in this trial.

DR. RUSSO: Okay. Well, I do think that, you know, being a female electrophysiologist, you know, women tend to probably gravitate to me more in general. So I probably do see a biased sample, and I see more women in general than probably, you know, the average electrophysiologist. I actually, you know, believe that actually some of the concerns that women have in general about, you know, body image, not that men can't have that either, of having a device in a different location that allows more privacy and if there is some cosmetic, you know, issues -- one woman I implanted had breast implants and was very much concerned about some of it, and obviously that's not what we're talking about today is cosmetics, but there are some reasons, and part of the reasons, and I will show you the x-ray here, part of the reasons why, you know -- we don't know why the reasons why women may not accept. Perhaps part of it is they won't accept ICDs as much as men. So I'm seeing a different -- more women than most people probably do in general compared to men, and, you know, I think it's a great option.

DR. ZUCKERMAN: So you would say that it's fair that in any proposed post-approval study, the company should target a certain number of female electrophysiologists to really --

DR. RUSSO: Absolutely. Thank you. And I could actually show you the numbers from the ICD Registry, if you want to see the comparison up there on your slide, but the registry, men are represented -- it's 74% basically. So we were pretty much what we're doing in real life here.

DR. LASKEY: Thank you. I have 10:00. I suggest we take a 10-minute break, and I will get started at 10:10. Thank you.

(Off the record at 10:00 a.m.)

(On the record at 10:10 a.m.)

DR. LASKEY: All right. Thank you all, and again, in the interest of staying on time, although, Dr. Zuckerman, I probably should get you a whistle. You sound like a camp counselor getting us back from break.

So it's now time for the FDA to give their presentation, and I will invite Ms. Terry to begin.

MS. TERRY: Thank you so much. Good morning. My name is Doris Terry. I am the Lead Reviewer for the PMA application, P110042, for the Subcutaneous Implantable Cardioverter Defibrillator, S-ICD System.

The FDA Review Team consisted of reviewers from offices within CDRH, the Office of Device Evaluation, the Office of Compliance, the Office of Science and Engineering Laboratories, and the Office of Surveillance and Biometrics.

In light of the Sponsor's presentation, I will provide a brief introduction of the S-ICD System followed by the clinical results and considerations by Dr. Brian Lewis, statistical considerations by Yao Huang, and post-approval study considerations by Dr. Shaokui Wei. The study conclusions will be presented after our presentations. After the break, FDA's summary prior to the Panel questions will be presented by Mitchell Shein.

The introduction of the S-ICD System includes the following: the proposed indications for use, the key regulatory milestones, device description, premarket study overview, preclinical and clinical testing, and the discussion points.

The proposed indications for use for the S-ICD System are as follows: The S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia that is reliably terminated with antitachycardia pacing.

The key regulatory milestones of the PMA application consisted of approval of the pivotal trial of the S-ICD System in February 2010, acceptance of the Sponsor's PMA shell for modular review in January of 2011, expedited review granted in June 2011, and receipt of the PMA application in December 2011.

The S-ICD System consists of the SQ-RX model 1010 pulse generator with firmware version 2.3.308.

When the device senses a ventricular tachyarrhythmia, it charges up to 5 maximum 80 J shocks. The device is programmable as a single shock zone where shocks are delivered based on the rate alone or conditional shock zone with discrimination algorithms. The device also provides post-shock pacing at 50 pulses per minute up to 30 seconds post-shock.

The system consists of the Q-TRAK Electrode, Model 3010, which utilizes the defibrillation coil, and sensing electrodes include the electrically active pulse generator can. Based on qualification testing, the electrode or lead has an operational life of seven years and is tunneled subcutaneously during implant with the Q-GUIDE Insertion Tool.

The system is programmed with the Q-TECH Programmer, Model 2020, with software version 1.85.00. The system also consists of various accessories which include the ECG Patient Screening Tool which is used to evaluate adequate sensing. This tool is intended to identify ECG characteristics which might result in suboptimal sensing of the S-ICD System.

Extensive preclinical testing was performed on the S-ICD System. The testing consisted of bench testing -- mechanical, electrical, and design verification testing on all system components including the lead; animal testing; biocompatibility and sterilization testing; software verification and validation; and EMC testing. All preclinical issues have been satisfactorily addressed with the exception of a battery issue that will be discussed on the next slide.

Before we begin our discussions today, regarding the clinical information, FDA would like to clarify two issues regarding the device battery. First, as noted in the Panel materials, there have been several cases of premature battery depletion reported. In June 2011, the Sponsor issued a field safety advisory about a premature battery depletion issue found in the investigational SQ pulse generators in the clinical study. FDA worked with the Sponsor to prepare a patient letter and make sure that regulatory bodies outside the U.S. were informed about the potential for premature battery depletion. Since the advisory, there has been one instance of battery depletion related to the field safety advisory. Additionally, there have been two other instances of premature battery depletion unrelated to the advisory. FDA continues to work with the Sponsor to understand the root cause of the premature battery depletion.

FDA will not consider PMA approval of the device until this issue is resolved. This issue is not the subject of the FDA's questions for the Panel. FDA asks that the Panel predicate their feedback regarding the safety and effectiveness of the device on an expectation that this issue will be resolved.

Secondly, FDA's review noted that the device has a limited service life compared to transvenous ICDs. At implant, the battery is capable of delivering 100 shocks. However, for an operational life of five years, the battery would have the ability to sustain the device's operation and deliver 21 shocks. If more than 21 shocks are needed, the operational life of the device would be decreased.

As will be discussed later in the presentation, FDA has asked the Panel to comment on the performance of the device particularly with regard to the observed inappropriate shock rate considering the limited service life of the device.

Clinical testing of the S-ICD System involved the IDE cohort, 28 U.S. institutions and 5 OUS institutions, and the non-IDE cohort which included chronic studies and registries.

The clinical testing consisted of patients indicated for an ICD based on the ACC/AHA/HRS indications. Type I clinical events, those events caused by the S-ICD System, which you will hear about later in the presentation, were used in assessing and supporting device safety. Acute induced conversion at implant with 65 J shocks induced either with the system or with catheter stimulation was used to support effectiveness. Chronic induced conversion and spontaneous episode treatment were also used in observational analyses to support effectiveness of the system.

The primary discussion points will include the patient population, observed clinical events such as inappropriate shocks, infection, and discomfort, the adequacy of the acute chronic and spontaneous episode experience, and evaluating device effectiveness, device labeling, and the post-approval study considerations.

Now, we will hear from Dr. Brian Lewis who will present the clinical results and considerations.

DR. LEWIS: Thank you, Doris. I'm Dr. Brian Lewis, FDA's

Clinical Reviewer for this original PMA. In addition to my role at FDA, I'm a practicing clinical cardiac electrophysiologist at the Washington, D.C. Veterans Affairs Medical Center.

In my presentation today, I'd like to give a brief overview of the Cameron Subcutaneous-ICD clinical study, including baseline characteristics of the enrolled subjects, implant experience, safety formal endpoint and observational data, effectiveness formal endpoint and observational data, and a summary of FDA's comments and conclusions based on our review of the trial.

This table provides a brief overview of the trial. This was a prospective, single-arm study to collect safety and effectiveness. Performance goals were developed based on extensive literature and publicly available trial results for the transvenous ICD. Adverse events were adjudicated by a clinical events committee. The target population included Class I, IIa, or IIb indicated ICD patients and patients with an existing transvenous ICD system who required replacement or revision. Screening was performed, as you have heard, using a proprietary tool to exclude subjects with unsuitably wide QRS or large T waves that might cause T wave oversensing or double counting.

Prior implanted bipolar pacemakers, but not unipolar pacemakers, were allowed in this study. When a S-ICD was implanted in a subject with a bipolar pacemaker, paced and intrinsic ventricular morphologies were collected and evaluated using the study's ECG screening method to exclude subjects whose pacing could cause trouble with double counting.

A similar evaluation was performed at implant. Also, symptomatic bradycardia and frequent pace terminable VT were excluded because this device cannot provide bradycardia pacing or ATP.

There were 28 centers in the United States, 2 Dutch centers, 2 New Zealand centers, 1 UK center, and those enrolled 330 subjects as you've heard. Nine patients withdrew prior to implant, leaving 321 implanted attempts of which 314 were successful.

FDA asked that the firm provide 100 implants followed to 360 days. FDA also asked for the measurement of at least 25 CPKs, creatinines, and chest x-rays perioperatively to assess for tissue damage, particularly skeletal muscle and alveolar hemorrhage from S-ICD implant test shocks. FDA asked the firm to perform conversion testing in at least 125 subjects at 150 days to assess the system's long-term effectiveness.

FDA and the firm agreed on a goal of the firm providing 50 reviewable spontaneous episodes of treated VT or VF to assess the response of the device appropriately recognizing and treating malignant tachyarrhythmias outside of controlled induction testing. The firm did adequately address these requests. This trial provided 109 spontaneous episodes. They occurred in 16 subjects. Sixty-eight of these had full reviewable data.

As I will mention several times today, there were 41 ventricular tachyarrhythmia or fibrillation episodes that all occurred in one subject as part of a VT/VF storm. These 41 episodes exceeded the memory of the device, and these 41, among the total in that patient, were overwritten and did not have reviewable data.

Here are all of the study objectives. The primary safety endpoint compared the 180-day system complication-free rate to a performance goal. As mentioned, the following safety data were analyzed using descriptive statistics, shock safety as measured by perioperative CPK chest x-ray and observed adverse events and inappropriate shocks.

The primary effectiveness endpoint compared the success rate of converting induced VF at implant to a performance goal. The following effectiveness data were analyzed using descriptive statistics: ability to implant the device without medical imaging is intended, success rate of converting induced VF at 150 days after implant, and the device response to spontaneous episodes.

Now, I'd like to show you an overview of subject enrollment implant attempts, successful implants, and subjects in active follow-up as of February 2012. I have indicated with shading the 321 subjects who underwent an attempted implant. This is the primary safety endpoint cohort. Please note that for the seven subjects who could not be implanted, in each of the seven cases, induced VF could not be reliably converted with a 65 J shock. These patients did not leave the hospital with the system implanted. In lighter shading below that, you can see the 314 subjects who had successful implants.

The primary effectiveness analysis cohort included those implanted subjects who also underwent testing for conversion of induced VF at implant where the testing was considered completed and evaluable.

Here are baseline characteristics of the study enrollees, which were similar to baseline characteristics of other contemporary ICD studies with the following comments. The average age as you have heard was approximately 52, which is younger than for other contemporary ICD studies. Approximately 26% of subjects were women, as has been discussed. Approximately 80% of implants were for primary prevention. The proportion of enrollees taking beta blocker was approximately 84%, consistent with adequate medical treatment of marked cardiomyopathy. Not shown on the slide, 26 patients or approximately 8% were on antiarrhythmic drugs.

As shown, approximately 43% of subjects had cardiomyopathy associated with coronary disease, and approximately 31% had non-ischemic cardiomyopathy.

Please note that the remainder of subjects in the trial were primarily due to hypertrophic cardiomyopathy, Brugada Syndrome, idiopathic VF and Long QT Syndrome. Forty-three of 321 subjects or approximately 13% had a prior transvenous ICD. Please note that of these 43 subjects with a prior ICD, 33 of 43 were removed for infection. Thirty-two of the thirty-three remained free of infection after implant of the S-ICD. One had a suspected infection reported one day after implant, which was treated with antibiotics and resolved fully within three days.

Now, I will show you safety results for the trial. Safety data were obtained for 50 subjects undergoing 65 J test shocks including creatinine, CPK, and chest x-ray as I mentioned. FDA review of this data did not find a suggestion of tissue damage.

Later today, the Panel will be asked to consider whether the firm's proposed post-approval study should incorporate objectives for testing for longer-term tissue damage, for instance, to assess patients with multiple shocks.

The next three slides discuss Type I, II, and III complications. As shown at the top of this slide, complications were defined as adverse clinical events that resulted in invasive intervention. Observations indicate adverse events that did not require invasive intervention.

As you have heard, the primary safety endpoint included only Type I complications which were adverse events requiring invasive intervention caused by the S-ICD. Type II complications were defined as those caused by misunderstanding or not following the S-ICD System user's manual or labeling. Type III complications were defined as those requiring invasive intervention that were not caused by the S-ICD System but would not have occurred in the absence of the system. I will provide examples in the next slides.

Here are the results for the primary safety endpoint in which 321 subjects with attempted implant were assessed for complication-free rate at 180 days. The Kaplan-Meier plot on this slide shows all Type I complications, again those defined as caused by the S-ICD System. The 95% lower confidence bound of the Kaplan-Meier Type I complication-free rate at 180 days was 97.9%. Therefore, the primary safety endpoint met its performance goal of greater than 79%.

As I will show you later, some Type II and III complications were regarded as worth considering, although they were not included in this endpoint.

This slide shows all Type I, II, and III complications limited to those that required either explant or surgery. Of the 10 Type I complications listed which were observed through the latest date of IDE data reporting, three were included in the primary endpoint because they occurred within 180 days. The other seven occurred after 180 days.

In the top rows, please note explants are shown. Shading indicates four infections requiring explant that were considered Type III complications. In the lower rows, please note that surgical revisions are shown. Lighter shading indicates a total of 12 cases that requires surgery to address problems with either lead or pulse generator position, lead connection, or wound healing.

Eight deaths were documented in the IDE study. FDA review of the information provided by the firm and adjudicated by the clinical events committee for six of the eight deaths show that the device functioned properly as intended and subjects were not resuscitable. One subject died of pneumonia; although device interrogation was not obtained, the following physician's assessment was that arrhythmias or S-ICD activity did not occur in this subject. As you heard from the Sponsor, one subject died during travel, and details for this subject's death are not currently available.

On the next slides, I will be discussing discomfort, infections, and inappropriate shocks.

The table on this slide shows all complications and observations associated with discomfort, infection, or inappropriate shocks. This data is through the latest date of IDE data collection. Note that complications shown in the second column included four instances of discomfort, one superficial infection, four system infections, and six inappropriate shocks. The next column to the right shows observations. Those are adverse events not requiring invasive intervention. Note that observations included a total of 19 instances of discomfort, 13 infections, 42 inappropriate shocks. Inappropriate shocks that were resolved with reprogramming were considered observations.

Here you see the frequency of discomfort and the treatments required to address discomfort. The largest section of the chart in blue shows that 300 of 321 implant attempts or approximately 93% had no reported discomfort. There are two smaller sections. The larger of the two in green shows that 17 or approximately 5% reported discomfort that resolved with non-invasive therapy alone. In the very smallest section in yellow, you see that 4 or approximately 1% reported discomfort that required surgery. Surgeries for suture discomfort occurred in two subjects and were successful. One device repositioning was successful to relieve bra discomfort. One surgery relieved hematoma-related pain. These adverse events resulted in adding a line to the list of potential risks for this device on the labeling, discomfort or prolonged healing of the incision. Also instructions for use were enhanced to address suturing technique. The firm has noted that training materials may be developed to address bra discomfort.

This slide shows infections and the frequency of various required treatments. The largest section of the chart in blue shows that 303 of 321 implant attempts or approximately 94% had no infection. The remaining 18 subjects are shown in four smaller shaded sections indicating treatments for infection. The smallest section in green indicates one subject whose infection resolved without antibiotic. Below that, the yellow represents eight subjects who required a single antibiotic. Below that, the orange section represents four subjects who required more than one antibiotic. And below that, the red section and red and white box indicates five subjects who required either explant or debridement.

Here you see explants performed for reasons other than infection. There were three explants performed instead of planned repositioning, including one for discomfort, one for pulse generator movement, one for suboptimal pulse generator position with difficult prolonged VF conversion testing. There was one battery depletion after a VT/VF storm. There was one requested explant against medical device [sic]. A single subject needed a CRT device, and a single subject required a device with overdrive pacing to suppress and prevent ventricular tachycardia.

In the next three slides, I'd like to discuss inappropriate shocks. The first shows the proportion of appropriate versus inappropriate shocks in the study. This trial included a total of 157 shocks. These occurred in 16 subjects. Based on what I have told you, about 68 confirmed episodes of VT/VF and 41 presumed appropriately treated VT/VF episodes, FDA and the firm considered that a total of 109 of the 157 shocks were appropriately delivered.

In the case of the subject with 41 presumed episodes that were part of a VT/VF storm, where the data exceeded the memory of the device, all episodes in this storm that had full data recorded showed appropriately detected and treated VT/VF.

As I described earlier, 48 of the 157 shock episodes in the trial were inappropriate shocks. So, in summary, approximately 69% of shocks were appropriate, and approximately 31% were inappropriate. This is consistent with the experience of appropriate and inappropriate shocks in other contemporary ICD trials.

This slide shows the frequency of inappropriate shocks according to their cause. A total of 48 inappropriate shocks were observed in the study. These occurred in 38 or approximately 12% of subjects. The chart shows the frequency of the two primary causes of inappropriate shocks. The largest section in blue shows the frequency of inappropriate shocks due to sensing of T waves, double counting, wide QRS complexes, or extra-cardiac noise. Noise of this type caused 28 of 48 or about 58% of inappropriate shocks. The smaller section of the chart in green shows the frequency of inappropriate shocks where SVT occurred with rates as fast as the rate defining the shock zone. The shock zone is the fast VT/VF detection zone. It uses rate alone as the criteria for distinguishing treatable from non-treatable arrhythmias. When SVT is detected and treated in the shock zone, this is considered normal device behavior although the shocks are not needed.

As the chart shows, the smaller top section, SVT with rates meeting detection in the shock zone accounted for 20 or approximately 42% of inappropriate shock episodes. As noted previously, in some subjects, the initial programming included only one VT/VF detection zone. For such subjects, the addition of a lower rate zone was often helpful.

A lower rate VT/VF detection zone includes advanced ability to discriminate SVT from VT/VF as you have heard by using criteria such as QRS morphology. Adding this kind of detection zone decreased the occurrence of inappropriate shocks and was recommended more and more as the trial progressed. Also, the firm has presented data to show that in some cases of inappropriate shock, the original screening ECG was borderline acceptable.

The efforts to increase use of the second advanced discrimination capability detection zone and adhere to the screening ECG protocol may inform efforts to ensure that labeling and training address these issues adequately.

This slide shows the frequency of various efforts employed to prevent the recurrence of inappropriate shocks when they occurred during the study. As shown by the larger section of the chart in blue, inappropriate shocks were prevented from recurring by simply reprogramming the device in 32 of 38 subjects or approximately 84%. As shown by the smaller section in green, 6 of 38 subjects or approximately 16% required more than simple reprogramming. These subjects required invasive therapies including thyroidectomy, AV node ablation, lead revision, MAZE procedure, and in two cases, explant of the S-ICD.

Here are the effectiveness data for the trial. As stated previously, the primary effectiveness endpoint compared the success rate of converting induced VF at implant to a performance goal of 88%. Here are the two key definitions for this endpoint. The definition of successful testing was two consecutive successes in the same polarity of four attempts. The definition of evaluable, as prespecified in the protocol, included only those implanted patients with complete conversion testing.

In this trial, according to these definitions, the protocol allowed for physicians to terminate testing early before it was completed or avoid testing entirely for any reason they believed was clinically necessary. Avoiding or terminating VF conversion testing early is sometimes clinically necessary in practice.

As shown on this slide, instances where testing was not completed included 16 subjects whose testing was stopped at the discretion of the treating physician, and of the 16, 11 had at least one failed shock. Five had difficulty inducing ventricular fibrillation. There was one patient that you've heard about with a left ventricular thrombus who did not have any VF conversion testing.

Here are the results for the primary effectiveness endpoint. The first two columns of the table show that among 304 evaluable subjects, all had successful conversion of VF that was induced at implant. This corresponds to a 95% lower confidence bound of the observed VF conversion effectiveness rate of 98.8%. This met the prespecified performance goal of 88%.

On the right column is the information I have previously shown you on non-evaluable cases for your comparison. Ms. Yao Huang, FDA statistician, will discuss a sensitivity analysis to include the 11 non-evaluable subjects with at least one failed shock as failures as well as a sensitivity analysis to include all 17 non-evaluable patients as failure. Whether you consider all 11 as failures or all 17, the primary effectiveness endpoint would still be met.

This slide shows the polarity and order of shocks in cases where VF conversion testing was completed and successful at implant. I'd like to remind you that the definition of successful testing for this analysis was two consecutive successes in the same polarity of four attempts. For example, in the first row, you see that 86.5% of subjects had successful conversion of VF on shocks number 1 and number 2, using standard polarity. On the second row, you see an additional 5% with failed first shock followed by successful second and third shocks.

FDA reviewed the data provided by the firm, describing the response time of the S-ICD delivering 65 J shocks for VF conversion testing. This table shows descriptive statistics for episodes, including all acute and chronic conversion testing. You see all VF episodes on the first row, then VT which was uncommonly induced, and then all VT plus VF episodes on the last line.

The second column shows that this includes 838 inductions. Note, in the third column, the mean time to shock, which you see are all approximately 15 seconds. In the last columns are third quartile values, most of which are near 16 seconds, and the maximum measured response times, some as long as 30 seconds.

FDA interpreted these response times for 65 J test shocks to mean that most of the time they will be delivered to treat VT/VF in approximately 15 seconds, which is favorable for resuscitation and survival. FDA interpreted the maximum response times for 65 J shocks to mean that infrequently patients with an S-ICD may receive 65 J test shocks after approximately 30 seconds.

The firm provided some explanation that these longer response times were owing to rhythms that were borderline for meeting rate criteria where the device oscillated between considering the rhythm treatable versus not treatable. FDA notes that this data was collected for 65 J shocks, and in the clinical environment, the device would need to deliver 80 J. These shocks may take somewhat longer to deliver.

As stated previously, the system was designed to be implanted without medical imaging, using anatomic landmarks only. This slide shows the majority of implants were accomplished without fluoroscopy.

Seventy-seven patients consented to conversion testing. This involved inducing VF at 150 days as you've heard and observing the S-ICD response. This was a descriptive statistics analysis in which the definition of successful testing was a single 65 J shock success, or if that failed, a single 65 J shock success in the reverse polarity. Seventy-four were considered evaluable. Three were considered non-evaluable. In all three non-evaluable cases, a single polarity was tested at 65 J with failure to convert followed by a successful conversion at 80 J. Testing was stopped at the discretion of the investigator. Per protocol, the opposite polarity should have been tested at 65 J.

Because the outcome in the opposite polarity is not known, these tests were deemed non-evaluable according to the definitions in the protocol. The observed success rate was 71 of 74 subjects or approximately 96%. As shown at the bottom of the middle column, these successes included 64 successes on the first shock, 7 successes on the second shock using reverse polarity.

Now, I will show you the results for spontaneous episodes. In this trial, 109 spontaneous episodes occurred in 16 subjects; 68 of the 109 episodes had full reviewable data as I mentioned before. Among these 68, 22 were monomorphic VT in 12 subjects. Forty-six were polymorphic VT or VF in six subjects. I have mentioned that 41 occurred in one subject. Two subjects had more than one rhythm. All episodes that were discrete, that is not part of a VT/VF storm, were successfully converted with S-ICD shock except one that terminated spontaneously, which was a monomorphic VT episode. All but one VT/VF storm episode was converted by the S-ICD. You've heard about that episode. It occurred in the emergency room using an external defibrillator while the S-ICD charged.

As I previously mentioned, 41 episodes did not have fully reviewable data. All 41 occurred in one subject as part of a prolonged VT/VF storm and related to the device limits of memory.

The S-ICD can demand pace at 50 pulses per minute up to 30 seconds after shock. This feature was programmed on in all but five cases in the IDE study. There were 183 instances of documented appropriate pacing and capture. There was one -- of inappropriate pacing without clinical consequences. FDA interpreted this data to mean that post-shock pacing functioned as intended.

I'd like to mention that we asked the Sponsor to look at whether gender or body mass index tracked with adverse outcomes. I won't read the entire slide, but I'd like to highlight that body mass index was not a significant predictor of outcomes, and female gender, as you've heard, tracked with discomfort with a four times higher likelihood of discomfort.

The firm is working with investigators to develop recommendations for implanting and following women to reduce their incidence of discomfort, and this may also be addressed through the post-approval study.

Here are FDA's comments and conclusions based on review of the IDE study's safety data. The S-ICD study met its primary safety endpoint. Shocks did not appear to cause myocardial or organ damage by perioperative CPK, creatinine, or chest x-ray. Discomfort occurred in 21 or approximately 7% of 321 subjects. Four required surgery. Infections occurred in 18, approximately 6% of subjects. There were five surgeries, including four explants. Explants for reasons other than infection were described.

Forty-eight inappropriate shocks occurred in 38 or about 12% of implanted subjects. Twenty were due to SVT that was detected in the shock zone and 28 for oversensing. Inappropriate shocks occurred more frequently with borderline ECG screening or single zone programming. Six of 38 subjects with inappropriate shocks required surgery. The remaining 32 were resolved by reprogramming. Overall, 48 of 157 shocks in the IDE study or about 31% were inappropriate.

The Panel will be asked to comment on whether the incidence of inappropriate shocks is acceptable and how the limited service life of the device impacts the Panel's assessment.

The Panel will also be asked for their recommendations for how to reduce the rate of inappropriate shocks and whether the Panel believes that labeling modifications to program a second conditional shock zone and physician training would help address this issue. The Panel will be asked whether the totality of the safety data provides valid scientific evidence that establishes a reasonable assurance of safety for this device.

Here are FDA's comments and conclusions based on review of the IDE study's effectiveness data. The primary effectiveness endpoint was met. The lower confidence bound of the observed success rate was 98.8% in 304 evaluable subjects. Seventeen non-evaluable subjects included 11 with at least one failed shock. Sensitivity analyses to include either 11 or 17 subjects as failures will be presented. These meet the performance goal. More than 86% of successful implant testing succeed on shocks number 1 and number 2 in the standard polarity. Implant without medical imaging was accomplished as intended in 304 of 321 implant attempts. Mean shock delivery time is approximately 15 seconds with some responses as long as 30 seconds; 71 of 74 subjects were successful at repeat VF conversion testing at 150 days; 109 spontaneous VT/VF episodes occurred in the trial, 68 of which had fully evaluable recorded data, showing S-ICD conversion in all but one that terminated spontaneously and one that received an external shock while the S-ICD was charging.

The Panel will be asked whether the data provided regarding induction testing in combination with the spontaneous episodes documented in the study provide valid scientific evidence that establishes a reasonable assurance of effectiveness for this device for detecting and treating tachyarrhythmias.

In addition to what I've pointed to in my Panel presentation that you'll be discussing this afternoon, FDA will also be looking for your input on the following topics: whether the proposed indications for use are appropriate considering the demographics of the population that was studied; whether there are additional subgroups who should not receive this device; whether the proposed labeling is acceptable or whether modifications are recommended including whether the labeling should specifically describe the differences and limitations of this device compared to transvenous ICDs.

The Panel will be asked to comment on what training and experience they believe is the most important and relevant for physicians to be qualified to implant the S-ICD. And in light of the proposed training program, and the information about the impact of the learning curve, the Panel will be asked whether there are information and/or recommendations for training that they would suggest.

And, finally, you will be asked whether the benefits associated with the S-ICD System outweigh its risks.

Now, I would like to introduce the next speaker, FDA's statistician for this submission, Yao Huang.

MS. HUANG: Good morning. My name is Yao Huang. I am the Statistic Reviewer for this PMA.

This is the outline of my presentation. First, I will introduce the study design for the pivotal study of the S-ICD System. Then I will present the analysis results of the primary safety and the primary effectiveness endpoints. And then I will wrap up my presentation with a summary of the analyses.

In study design, the pivotal study for the S-ICD System was a prospective, multicenter, single-arm study. A total of 33 centers participated in the study. Among them, there were 28 sites from the United States and 5 sites from outside the United States.

The study has two prespecified primary endpoints, one for safety and one for effectiveness. The primary endpoints were compared against prespecified performance goals. The primary safety endpoint is defined as complication-free rate at 180 days post-implant. The performance goal for this endpoint is 79%. The primary effectiveness endpoint is acute induced conversion rate. It was compared against a performance goal of 88%. The study needs to meet both the primary safety and the primary effectiveness endpoints.

And the study also planned to collect data on chronic device performance in two aspects. One is to observe the continued chronic performance of the Subcutaneous-ICD system during appropriate device detected episodes of VT/VF. The Sponsor would provide 50 spontaneous episodes for this outcome. Another chronic outcome is to observe the continued chronic performance during induced episodes of VT/VF at least 150 days post-implant. The Sponsor would provide 125 chronic performances for this outcome. The data on chronic device performances have been presented by Dr. Lewis in previous slides.

Clinical data. The cutoff date for the clinical database was February 14, 2012. The study enrolled 330 patients. Nine of the enrolled patients withdrew from the study prior to the implant procedure. Among the 321 patients with an implant attempt, 7 patients were not successfully implanted.

Analysis of the primary safety endpoint. This is the analysis for the primary safety endpoint, which is defined as complication-free rate at 180 days post-implant. The total analysis cohort includes the 321 patients with an implant attempt. Among these patients, 3 patients reported with Type I complications, 15 patients dropped out of the study prior to the 180-day visit, and 30 patients stayed in the study but had not reached the endpoint when the clinical database was closed. Therefore, the estimated Kaplan-Meier complication-free rate at 180 days is 99.0% with a 95% lower confidence bound of 97.9%, which met the performance goal of 79%.

Missing data for the primary safety endpoint. As indicated in the previous slide, 45 patients either dropped out or were censored by 180 days. A closer look at the 15 dropouts shows that 7 patients were not implanted, 5 patients did not experience any Type I complication, but later on, when explanted, prior to the 180-day follow-up visit, 3 patients did not experience any Type I complication but died prior to the 180-day follow-up. The 15 dropout patients were treated as failures in the sensitivity analysis in the next slide.

Sensitivity analysis for the primary safety endpoint. This analysis treats the 15 dropouts as failures. Therefore, there are 18 Type I complications, including 3 observed and 15 imputed. Thirty patients were censored at 180-day follow-up. The estimated Kaplan-Meier complication-free rate at 180 days is 94.3.% with a 95% lower confidence bound of 91.7%, which met the performance goal of 79%.

Clinical data for the primary effectiveness endpoint. This table lists the effectiveness outcomes of all 321 patients with an implant attempt. Among those patients, 304 patients completed the four testing protocols for acute conversion. Eleven patients failed to complete the entire battery of conversion testing but had at least one failed shock. For five patients, all shocks delivered by the S-ICD System converted the induced arrhythmia, but testing was not completed. One patient did not undergo the conversion testing at the discretion of the investigator.

The FDA believes the effectiveness analysis should include the 304 patients who completed the four conversion testing and the 11 patients with at least one failed shock during the conversion testing.

Sponsor's analysis of the primary effectiveness endpoint. The

Sponsor indicated that one patient did not go through the conversion testing under the clinician's discretion, and other 16 patients were believed as non-evaluable. Therefore, the Sponsor's analysis was based on the 304 patients who had successful conversion testing. The analysis provides an estimated success rate of 100% with a 95% lower confidence bound of 98.8%, which met the performance goal of 88%.

Here is another analysis of the primary effectiveness endpoint, which the FDA believes is more appropriate for the effectiveness assessment. It is noticed that among the non-evaluable patients, 11 patients had incomplete conversion testing with at least one failed shock, and the FDA believes these patients should be included in the analysis as failures. Therefore, the estimated success rate is 96.5% with a 95% lower confidence bound of 93.8%, which again met the performance goal of 88%.

A worst-case analysis was conducted for the primary effectiveness endpoint. The analysis includes all 321 patients who went through an implant attempt. The 17 non-evaluable patients in the Sponsor's analysis were treated as failures here. The estimated success rate of the worst-case analysis is 94.7%, with a 95% lower confidence bound of 91.7%. The performance goal of 88% was met according to this analysis.

To summarize the data analyses, the study met the performance goals for the primary safety endpoint and the primary effectiveness endpoint. The sensitivity analyses also showed that the performance goals were met.

Now, Dr. Wei will discuss issues related to the post-approval study proposed by the Sponsor. Thank you.

DR. WEI: Good morning. I'm Dr. Shaokui Wei, an epidemiologist in the Division of Epidemiology, Office of Surveillance and Biometrics.

Today I will talk about the post-approval study that has been proposed for the S-ICD System submitted by Cameron Health, Incorporated. The presentation is based on the post-approval study outline dated March 12, 2012.

Reminder. Before we talk about the post-approval study, we need to clarify a few things.

First, the discussion of a post-approval study prior to the FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

Second, the plan to conduct a post-approval study will not decrease the threshold of evidence required by FDA for device approval.

Third, the premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and the appropriate risk/benefit balance.

Need for post-approval studies. Please note post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of reasonable assurance of device safety and effectiveness.

The reasons for conducting post-approval study are to gather postmarketing information including:

First, long-term performance of device.

Second, data on how device performs in the real world in the broader patient population that are being treated by community-based physicians and specialists, as opposed to the highly selected patients treated by investigators in the clinical trials.

Third, evaluate effectiveness of the training program for use of devices.

Fourth, evaluating device performance in the subgroups of patients since clinical trials tended to have limited numbers of patients in certain vulnerable subgroups of the general patient population.

And, finally, to evaluate outcome of concern regarding the postmarket safety and the effectiveness of device, for example, rare adverse events.

In addition, the post-approval study can also address any other issue that may be identified by the Panel members based on their experience.

Important postmarket issues. A thorough review of the premarket data, FDA has identified the following concerns that will need to be addressed in postmarket.

First, assessment of long-term performance of the device, since the premarket follow-up was only 180 days.

Second, assessment of device performance in the representative population of providers and patients because IDE patients were relatively young and have mild heart dysfunction and were treated by highly trained investigators in the clinical trials.

Third, to assess if there's a difference in the safety and the effectiveness -- as suggested by small numbers in the premarket -- data.

Fourth, evaluation of long-term performance with respect to the battery performance, therapy delivery, RF telemetry and software/ firmware performance. FDA recommends the IDE patient be followed every six months for at least a period of three years.

Finally, include the evaluation of lead safety up to five years in the post-approval study.

Now, I will present an overview of Sponsor's proposal.

The Sponsor proposes to conduct a prospective, multicenter, observational study to evaluate long-term safety of the S-ICD System.

The only primary endpoint which will be examined is the 36-month complication-free rate as defined within the IDE study. Complications are those clinical events specifically caused by the S-ICD

System and requiring invasive intervention or resulted in death.

The study population will be all patients implanted with the S-ICD System who provide a written, informed consent, which consists of the patients initially implanted with the S-ICD System in the premarket IDE study, about 300 patients. And an additional prospectively enrolled cohort, from approximately 50 U.S. clinical centers, about 470 patients. The overall sample size is 800.

Follow-up. Data will be collected and entered into the NCDR ICD Registry to evaluate perioperatively six months and annually through five years.

The proposed hypotheses is the 36-month complication-free rate of the S-ICD System, p1, but not exceed the performance goal p0. p0 is the 36-month performance goal based on adjusting for 79% 6-month threshold downward to account for additional expected events between the 6 to 36 months. p0 was not specified by Sponsor.

p1 is the true 36-month complication-free for the S-ICD System for the patient enrolled prospectively in the post-approval study.

Besides endpoint estimate, the Sponsor also proposed to conduct the following:

Non-endpoint evaluation.

The long-term safety: Comparison between IDE and the post-approval study cohorts. The six-month to five-year complication-free rate data for the new post-approval study cohort will be compared with the initial IDE study.

Long-term safety: Comparison to the transvenous ICD data in the matched population.

Five year mortality estimate. Post-approval study will provide mean to collect additional mortality data in the patient implanted with the S-ICD System over the five-year follow-up period.

Long-term effectiveness: First shock and episodic conversion. First shock and episodic conversion will be calculated through a collection of the spontaneous episode reports throughout the study period.

Subgroup analysis by gender. Subgroup analysis will be performed for each endpoint on the non-point evaluation by gender. However, the Sponsor did not provide details of how they will conduct this non-endpoint evaluation.

Now, I would like to move to the assessment of the post-approval study proposal. The Panel will be asked to discuss this issue in the afternoon session.

First, the follow-up duration is five years, yet the hypothesis is tested at 36 months. FDA recommends that safety and effectiveness should be formally assessed through a hypothesis test at five years.

Second, the performance goal is not specified. FDA recommends the performance goal be specified based on the observed 6-

month safety performance (complication-free rate of 98%) to estimate the 60-month complication-free rate of the S-ICD System.

Third, long-term effectiveness will be assessed in non-endpoint evaluations. FDA recommends that the long-term effectiveness be evaluated as the primary endpoint with the hypothesis.

Fourth, there is no assessment of device performance with respect to the battery life, therapy delivery, RF telemetry, and software/firmware performance in the post-approval study. FDA believes that patients enrolled in IDE study should be followed every six months for at least a period of three years to evaluate this long-term device performance.

Fifth, there is no assessment on adverse events included in the post-approval study protocol. FDA believes that all adverse events that are related to the procedures, devices, and the patient's condition should be reported in the post-approval study.

Sixth, consistent with the post-approval study, transvenous ICD data, the post-approval should include evaluation of the S-ICD System lead complication-free proportion at five years.

Finally, the NCDR ICD Registry collects the baseline patient demographics and the procedure related to adverse events only. The post-approval study plan does not provided details on how they will conduct longitudinal follow-up for the study participants. FDA believes that the

Sponsor should provide the details on how they will monitor study participants in the post-approval study throughout five years.

Now, Ms. Terry will give the study conclusion.

MS. TERRY: Thank you, Dr. Wei. As we've discussed, the primary safety and effectiveness endpoints were met. FDA's presentation discussed other elements of the study datasets that we believe are applicable to questions regarding safety and effectiveness.

So at this time, thanks for your attention, and we look forward to a productive Panel discussion.

MR. SHEIN: So I'm Mitchell Shein. I'm the Branch Chief for the Pacing, Defibrillation and Leads Group. We're now ready to address any questions you might have for us.

DR. LASKEY: So, first of all, thanks to the FDA for a very helpful presentation. Before we open up to the floor, I just wanted to ask our statistical friends to just comment on the appropriate unit of analysis here. So we have multiple events in a given number of patients. The OPCs are per patient I would assume, but is there a way of looking at the distribution of shocks. If you take out the one patient with storm, could we look at the distribution of shocks across this sample, number one. And, number two, can you just weigh in on the use of, the appropriate use, the statistical analysis of per patient versus per shock in terms of these OPCs?

MR. SHEIN: Dr. Lewis, would you like to address that please?

DR. LEWIS: I'd like to be sure I understand your question. So the OPCs referred to proportions of the population. Does that answer your question?

DR. LASKEY: Per patient, right.

DR. LEWIS: Patients were individually scored as successes on either safety or effectiveness but --

UNIDENTIFIED SPEAKER: It is per patient, not per shock.

DR. LEWIS: Right, right. You're asking for was the proportion of patients.

DR. LASKEY: That I understand, but when you have events which are clustered within patients, there are other ways to look at rates.

DR. LEWIS: Right, right. I think that that's correct. It was simply per patient.

DR. LASKEY: In anticipation of post-approval study where we're going to have many more patients, is this worth discussing, further looking into or looking at, just look at the distribution of events across the number of patients?

DR. LEWIS: Right.

DR. LASKEY: Are they clustered within a small subpopulation is the point here?

DR. LEWIS: Of course. I think the answer is of course.

DR. LASKEY: Right.

DR. ZUCKERMAN: So, Dr. Naftel, can you provide some insight? Should we be using a GE approach, or how do we handle the clustering?

DR. NAFTEL: Well, it's a great and obvious question. Certainly from my perspective, the per patient is where I would start, but as you're indicating, all the discussions through the years on linearized rates with thrombosis after valve surgery or whatever, those are all rates that look at multiple events in a patient, but then when you have, you know, a statistically weird thing like this, with the storm in that one patient, and it just -- if you did a rate, it would just totally overwhelm the whole analysis with that one patient, but nevertheless, I would want to do exactly what I think you're asking for. Look at a distribution of the shocks across patients, look at maybe the Nelson Method for accumulative events across time. I would want to look at it both ways is my -- that's my answer, Dr. Zuckerman.

DR. ZUCKERMAN: Thank you.

DR. LASKEY: Okay. Back to the Panel. Rick.

DR. LANGE: Two questions to the FDA. The first relates to the lead life, which was identified as seven years, and if you could this afternoon tell us how that was arrived at, and you may pass that off to the Sponsor. That's fine. But I'd be interested in knowing how we arrived at that. I can understand how we get battery life. It would be interesting to see how lead life may be seven years.

And my other question relates to the battery depletion, and I realize we're not to address that. You all are addressing that, but specifically I want to make sure that the FDA is identifying all those, and what I'll do is I'll refer to the Sponsor's Executive Summary, to two pages, page 102 and to page 94, and both the Sponsor and the FDA identified two battery depletions, premature battery depletions, but it appears there's three as far as I can tell. And one of those is categorized as an inability to communicate with the pulse generator. So, again, I don't think anybody's being deceptive. I don't think they're trying to hide anything. It's just that it falls in a different category. I just wanted to make sure that you guys are identifying all the battery depletions, and I can give you specific patient numbers if that would help.

MR. SHEIN: On the battery depletion, I think that there was the one that you recognized, but there was another issue for which the advisory was sent out, and that dealt with a design issue within the battery cell itself, and we continue to work with the firm to make sure that that correction, the corrective actions that they've taken adequately address that, and that's why we feel that that's not something that we need to be discussing or have you deliberate on that we wanted you to be aware of. It will absolutely be addressed before I would be willing to consider signing off on an approval for the device.

DR. LANGE: Great. And, again, I don't want to issue the issue of battery depletion, but both you and the Sponsor have identified two patients, but I see three here, and so I just want to make sure that you're capturing them all.

MS. TERRY: Yes, we do know that there are --

DR. LANGE: Okay.

MS. TERRY: -- four, a total of four. So we have the correct numbers.

DR. LANGE: Great. Thanks.

DR. ZUCKERMAN: Dr. Lange, thanks for asking those two critical questions because I do think we need more discussion of the lead both by FDA and the Sponsor this afternoon, but perhaps as a prelude to allow you to perhaps add to your question, can we have Ms. Erin Cutts come up and show your preliminary slide?

MS. CUTTS: My name is Erin Cutts, and I did the engineering review of the lead for this system. I actually don't have a preliminary slide. There were some questions about what the cross-section and the different materials were used in the leads. So I've prepared, you know, kind of background on that, that I'd be happy to discuss in general. In an hour, I'm sure we could put together a slide to go over after the lunch break.

I was going to touch slightly on your question about the lead durability, the life. From what I understand, there was a number of fatigue tests that were done on the lead. It's in a different location than a lot of the transvenous leads. So the testing isn't necessarily for, you know, how often the heart beats but more often how many breaths you're going to take and the different types of loads that would be on the lead based on the location that it's in. Those fatigue tests were based on 10 years from what I understand, you know, how often you breathe over 10 years, how often you might be expected to lay down or press on your chest in that period of time, and I believe the Sponsor has taken a conservative approach at backing that down to 7 years. So that's my understanding of where that came from.

DR. ZUCKERMAN: So would it be okay, Dr. Lange, if the Sponsor then gives additional details after lunch to allow them to respond?

DR. LANGE: Yeah, that would be great, and as you allude to, it's in a different place, and so there are different stresses. There are seatbelts and breathing and soccer games and I don't know what else but -- so I'd just be interested in knowing how you all arrived at that jointly. Thanks.

DR. LASKEY: So, just so we're clear, what do you want the Sponsor -- what would we like the Sponsor to come back with this afternoon in terms of lead integrity? The preclinical data or something additional.

DR. SOMBERG: Can I ask a question just related to this before you do that? Because I'm not sure what that means that it has seven years. Is the Sponsor or the FDA recommending that that be taken out and replaced at seven years, or is there a test? So I mean that's part and parcel to it. Is there an evaluation of it in some way or does at seven years -- and hopefully all these patients get to seven years, but at seven years, does it need a transfer, and how difficult is that transfer? I mean there's going to be some fibrosis, et cetera. Has anyone addressed that?

MS. TERRY: I think that the Sponsor can speak to this because they are saying upon change out you should check the integrity of the lead. So I think this is a subject that they can speak to considering the declared --

DR. SOMBERG: You have to be cautious though. The change out is going to be in about five years for the generator. It's --

MS. TERRY: Exactly.

DR. SOMBERG: -- and so you have two years. I mean bring someone in at two years again, that's a -- and I would imagine the surgical replacement of that is going to be harder than the initial insertion of it. So -- and I'm not sure you have to change it, you know, at this point.

MS. TERRY: Right.

DR. SOMBERG: So this might -- so these are things that should be addressed --

MS. TERRY: In the event.

DR. SOMBERG: -- by the Sponsor.

MS. TERRY: They can address that.

DR. LASKEY: Just so we're clear, because I'm not, what are we asking the Sponsor to come back with?

DR. ZUCKERMAN: Dr. Laskey, how about at a minimum as we heard from Ms. Cutts, the lead is in a different position with different stresses. So, one, the Sponsor will help justify their preclinical testing in their average lead estimate of seven years. They will also try to address some of Dr. Somberg's key clinical questions regarding how should the lead be followed? What happens when you need a replacement lead, et cetera? And then the FDA will make additional comments if necessary, but the bulk of the presentation will be given by the Sponsor.

DR. LASKEY: In the interest of clarity, do we know whether the FDA's bench testing was done in the configuration in which it will exist in vivo, i.e., with this 90˚ or U-turn? How do you exactly do the bench testing knowing that there's a fairly robust angle there?

DR. ZUCKERMAN: All right. I think that also is a question for the firm to address. They've designed it, and we've just evaluated it in the reports.

DR. LASKEY: Fair enough. Dr. Milan.

DR. MILAN: I'm curious where this performance goal of 88% came from. I mean the transvenous systems that we use have been around for many years. There's thousands of patients' data. If you looked at large clinical trials and large clinical experience with these devices, the success of defibrillating patients with newly implanted transvenous systems with a 10 J safety margin is 98% roughly, 97-98%. So I'm just curious how 88% became the performance goal for acute VF conversion success for this device.

MR. SHEIN: Dr. Lewis, you want to try to address that.

DR. LEWIS: So there are two things that I would say. One is that the success of VF conversion was very high during the trial. So we can talk about the bar that it may or may not have met, but it was actually observed to be a very high rate. That's number one.

Secondly, it was based on review of the literature and a discussion with the Sponsor. So --

DR. SELZMAN: Just to add to that, so I'm Dr. Selzman. I'm Chief of EP at the Salt Lake City VA, but I am also a Medical Officer for the FDA, and I was involved in some of the discussions with the Sponsor at the time of IDE application. And so there was a lot of discussion back and forth on the safety performance goal as well as the effectiveness performance goal, and what we did is we went back and looked at a lot of older studies. And so there was a range of studies from more recent to a little bit older studies, and so that's why the performance goals might seem a little low.

So, in addition, for example, the safety endpoints, of course, the potential risks with implant of this device is going to be different than with a transvenous system. You're not going to a pneumothorax or perforation and things like that.

So because this is a novel system and in some ways not very comparable to a transvenous system, it was hard to come up with numbers.

So we ended up using, you know, transvenous data but not just the most recent, some older studies, too. So that's where the numbers came up at, and we all agreed upon.

DR. MILAN: Just to --

DR. LEWIS: One more comment on that.

DR. MILAN: Sorry.

DR. LEWIS: So now that this base of information, the rates have been characterized, that will be very helpful for moving forward, for instance, for setting bars for the post-approval study.

DR. MILAN: All right. So just to follow up, I mean I agree with you. If you accept a 100% success rate for efficacy, then you could set the bar wherever you want, but if you start to look at some of the sensitivity analyses where you start to include the patients who were non-evaluable, you're now with confidence levels extending down into the low 90s, and I think it does matter.

DR. LEWIS: Right. And, of course, there's always going to be lessons about non-evaluable that feed into the next trial design.

DR. LASKEY: So the point's well taken, but hopefully we won't revisit it. This was a previously agreed upon number between the Agency and the Sponsor, but the point's well taken. It may be a moving target going forward. Other --

Dr. Somberg.

DR. SOMBERG: The epidemiologic discussion I think was most useful about the proposed postmarketing study, and that goes into the performance threshold because it says here on slide 11, I'm sorry, 71, I can't see here, 71, it says that the Sponsor proposed adjusting downward, and I would say in light of the presentations, as you were saying as well, that that actually should be adjusted upward, and it's also very important to put in the adverse events as well as the efficacy, especially since it's going to be put in a registry, and in this situation, the registry has agreed to provide I believe efficacy and safety data unlike other situations. So you have to capture that data. It would be very important for comparative purposes.

DR. ZUCKERMAN: Dr. Somberg, those are very important points, and there is a Panel question on that subject as you point out, but one thing for the Panel to consider when they get to that question this afternoon is the performance goal as set up right now only includes Type I events, and that's fine for the purposes of this study, but as noted in the trial, Type III events included infections which required device explant. You can also review some of the Type II complications, which were quite significant.

So another way for the Panel to think about this is whether Types I through III complications should be all grouped together, and that will determine a different type of performance goal and so forth, but that's a question for this afternoon.

DR. SOMBERG: Obviously those are very important things, but one of my observations was you have to be careful with infections because I was impressed that we didn't have systemic infections, and I think that's one of the advantages, and also that there were a lot of people who were explanted from transvenous systems who went to this. I think that will be an important potential niche for a product like this. So how you weight those two is going to be another question because, you know, just giving my opinion, I'd rather have, you know, a superficial infection than endocarditis or something and having dealt with patients who -- in fact, having a patient that maybe I caused, that's quite a severe problem.

DR. ZUCKERMAN: Appropriate points, but when there's an infection that requires device removal, with this particular device, you know.

DR. LASKEY: Dave.

DR. MILAN: It looks like on FDA's slide number 19, that the target sample size and data included greater than or equal to 125 VF conversion tests at 150 days. However, it looks like to me anyway, there were only 77 presented, but I didn't hear anybody at FDA bring that up. Are you happy with 77 instead of greater than or equal to 125?

MR. SHEIN: I'll start with that and then turn it over to the clinicians to comment.

DR. SELZMAN: So, again, in discussions with the Sponsor at the time of IDE submission, FDA felt that we wanted a certain minimum number of chronic conversion testing. The 125 was a little bit arbitrary to be honest, but we thought it was a reasonable percentage of the total cohort that would give us comfort level in terms of chronic performance of the device.

When the IDE concluded, when the study was terminated by the Sponsor, you're right, that there were 77. I wouldn't say that we happy or unhappy, but that's what we have in, but the tradeoff that the Sponsor did point out to us is that there were more spontaneous episodes than we thought we would get. So there is less chronic conversion testing but more spontaneous.

Having said that, there is some clustering in a few patients, and if you deleted that, the total number of patients with spontaneous episodes is what I would say on the small side. So -- and also in discussions with the Sponsor, you know, they communicated to us that they just had difficulty getting people to kind of sign up for this part of the study. So --

DR. LASKEY: It's real life stuff. Okay. Any other? It would be astonishing if we were to break for lunch and stay early rather than on time or late, but are there no other questions for the Agency?

Then if not, I have 11:30. I suggest we have a one-hour lunch, and we'll see you all back at 12:30 promptly.

Thank you very much, Sponsor and the FDA.

(Whereupon, at 11:30 a.m., a luncheon recess was taken.)

A F T E R N O O N   S E S S I O N

(12:31 p.m.)

DR. LASKEY: Thank you for getting back on time, and I'd like to resume the Panel Meeting with the Open Public Hearing portion of this meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views which are relevant to our meeting agenda today.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. LASKEY: It's my understanding that there has been one request, and I would ask Ms. Lisa Williams to come to the podium to make her presentation.

MS. WILLIAMS: Good afternoon. My name is Lisa Williams, and I do not have any financial relationships with any parties associated with this today.

I am a patient that has received a Subcutaneous-ICD system, and I've also had a transvenous ICD system. I will let you know that my training and my professional background is in the medical device biotech arena, and so that's why I'm interested in being here today, to share my perspective as a patient.

So in October of 2010, I received the Subcutaneous-ICD system in conjunction with a full system extraction of a transvenous ICD system. The transvenous ICD system that I had was as a primary prevention patient in 2005 due to an underlying cardiomyopathy with a very strong family history of sudden cardiac death pervasive in my family.

So the reason for the Subcutaneous-ICD system was I had experienced several complications with the transvenous system, complications that included me being placed on pharmaceuticals that I didn't ultimately need to be placed on, having some venoplasty procedures from what was perceived to be some occlusion issues, SVC syndrome I believe is what they called at the time, and ultimately I had a lead failure that resulted in inappropriate therapy multiple times, and that's why the system was fully extracted.

So when I was faced with having my second ICD at the ripe old age of 35, I did some research to look at what my options would be, and thankfully the Subcutaneous-ICD system was approved as part of this IDE study at my local heart hospital.

So I'm here just to interestingly share my perspective as having both a transvenous system, a subcutaneous system, and with some of your questions directed primarily towards a female patient population, I'd be happy to share my perspective in that as well, and just to let you know, that I am thankful that this alternative and this option was available to me when I needed this option, and I hope to have several gen changes throughout the years. So I hope it continues to be an option that's available for me, my family members, and the public at large. Thank you.

DR. LASKEY: Lisa, thank you. I don't believe that there's any questions on the part of the Panel? No.

Thank you so much for coming forward.

With that, I'd like to -- is there anyone else who wishes to approach the Panel?

If not, I'd like to pronounce the open public hearing to be officially closed, and let's proceed with today's agenda.

We'll begin with the open Panel Deliberations, one of the funner parts of our job. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Chair.

Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist to identify the speakers.

So during the next hour, we will open up the floor to questions for both the Sponsor and the FDA.

So, first of all, if the Agency or the Sponsor were asked questions to respond to, during this portion they may do so now. In any case, the Sponsor should go first.

MR. MARCOVECCHIO: Thank you for the opportunity to address some additional questions that you had this morning. Your first question from Dr. Lange was regarding whether or not we had any information pertaining to the height and COPD as it might affect impedance, and I'd like to invite Dr. Burke to provide that information for you.

DR. BURKE: I am Dr. Martin Burke. In the opening statement, in the core lecture and review, I demonstrated demographics on patients, but I did not specifically identify how many patients were actually suffering from COPD, and in this case, if you look at this slide, n was 27 for a total number of 8%. In this particular study, we noticed that the IDE study, the shock impedance at induction testing had a mean of 78.8 Ω, and that this was distributed in a 40 to 140 Ω range, which is not unusual for a single coil to can distribution. And we did not specifically see any differences in the COPD patients or based on height, and when you look at safety metrics as well, COPD and height had no differences across the entire spectrum, nor did the effectiveness in those two groups.

MR. MARCOVECCHIO: Alan Marcovecchio, Director of Clinical and Regulatory Affairs from Cameron Health.

The next question that we had captured from this morning's discussion was regarding a bit more information on the ECG screening, patient surgical preparation and dual chamber pacing, dual chamber programming, excuse me, with regard to how that would be communicated in the labeling, and I'd like to invite Dr. Gold to address those matters please.

DR. GOLD: Thank you. I'm still Michael Gold.

With regard to the aspects of prepping the patients, to start with, while we've mentioned that this is similar to transvenous procedures, this actually is a new operation for everyone who does this procedure who's put in transvenous devices. The prep area is larger than with transvenous implantation, and the location of the pulse generator, as we've already mentioned, is more in the flank than up in the pectoral area, and the electrode incision points are different. So it requires a more extensive prep area, extending more lateral than we typically do it.

This was a new procedure at all centers, and again the learning points that we had from this was that we needed to communicate better these preparation and how to prep these patients, which was done formally at our meeting. We had an investigators' meeting, and which we think is certainly one of the reasons why there were no device explantation for infection in the last two-thirds of the study, and this has already been put into the manual for patients, the manual for physicians, sorry, for implantation.

I'd like to move on now to the second question which was the question about dual zone programming. Again, we recognize that dual zone programming was important when we looked at inappropriate shocks, and if we look at the inappropriate shocks for either oversensing or for supraventricular arrhythmias, we can see quite clearly here that there was a more than 50 percent reduction in those patients who had dual zone programming, and there was an almost 75% reduction in supraventricular arrhythmias for those who had dual zone programming. So we felt strongly again that the dual zone programming was very effective. This was another one of those learning experiences that we had early in the study that we communicated at the time of the investigators' meeting and led to much more extensive use of dual zone programming. So if you see the ends there on the bottom, again we can see that there's a much larger number of patients who ended up with dual zone programming once that had been communicated.

Just to show for people, who may be used to ICD programmers which can be fairly complicated, I think most of us who use them get used to it, but this is a very, very simple, essentially single button where you just slide where you want your first zone, where you want your second zone, and with that you simply have completed your programming and set up automatically a dual zone programming set for these groups of patients. And, again, this will be in the physician's manual for this device, both how to use it and the recommendations to use it.

Moving onto the third question I think that I was asked to address, which was the screening tool, there were two patients in the IDE study which were already mentioned who had oversensing issues who required explantation of that. A retrospective analysis showed that they were borderline by the screening tool. It turns out that this could be solved not by any change in the screening tool itself, but rather than just using one beat, use a series of beats on the electrocardiogram to make sure that they consistently fall within the screening tool, and when this was applied retrospectively, these two patients would not have been approved for the study, and there were seven other patients who were in the study who would have also been screened out. But, again, this is not any change in the screening tool itself, but a change in the rules. Rather than use one beat, use a series of beats so you're comfortable that that would be done, and again this has already been put into the manual, the physician's manual of how to use the screening tool we think in the most efficacious way to avoid any of these unfortunate complications.

And the data here is that a total of nine IDE patients were identified that would have failed including those two patients, so that with these updated instructions, about 2.2 percent of patients, additional patients would not have been included in this study, but we think that's a small price to pay probably for having eliminated those groups of patients who ended up having an explant for inappropriate therapies.

So with that, I'd like to turn back to Mr. Marcovecchio so we can continue to go through the questions.

DR. LASKEY: Before that, one correction for the transcriptionist. Several people have used the term dual chamber here and, in fact, it should reflect dual zone, is what Dr. Gold was addressing here.

MR. MARCOVECCHIO: Thank you. The next question was regarding whether or not there was any instance of twiddling with the system. Additionally, was there any information on body mass index, and I'd like to invite Dr. Burke to answer those two points please.

DR. BURKE: The answer to the twiddling question is, no, there were no episodes of twiddling. There was some slight movements in the pulse generator that were addressed with revisions, but none for twiddling.

The second part of the question relates to just the interaction of the device system and lead system based on BMI, and you can see that the distribution of BMI as mentioned earlier by one of the Panelists was at about 30 in mean, but in actuality, it had a wide expanse in this particular population in the IDE, and we definitely had a wide variety of patients that ranged from less than 16.5 BMI all the way up to greater than 40.

And the one thing that you can say about this device is that one size fits all, and there was not a necessity for a big variation in the can; the lead system, the lead length, the stability of the system, the ability for the lead system to be effective and safe across a wide BMI is extremely stout, and we feel very good about this after this large IDE study that we can make this statement across a very wide BMI.

MR. MARCOVECCHIO: Dr. Milan raised a matter this morning regarding recommendations for patients who could not be converted at the maximum output and whether or not there was any additional information we had regarding difficult conversions and the possibility for rising thresholds. I'd like to invite Dr. Gold to present a bit more information in response to those comments from this morning.

DR. GOLD: Yes, we started to address some of the concerns about whether there was a rise in defibrillation thresholds or a decline in defibrillation efficacy over time in this group of patients. And we actually calculated the data to make it an apples-to-apples comparison because the algorithms, the protocols were different at implant compared to at follow-up, which we had mentioned. So I'll just quickly take you through this 2 by 2 table. So if we look at first shock efficacy at 65 J at the first polarity tested, at the acute conversion testing was 89.3%, at the chronic conversion substudy was 87%.

We could switch polarity. So if we now switch polarity and look at the first shock efficacy at final polarity tested, for the acute conversion testing it was 91.2%, and for chronic conversion substudy it was 92.2%. So really there's no signal at all, no difference in the efficacy when we're comparing sort of identical testing protocols.

We have data which I wasn't going to spend a lot of time going through, but if you actually go through clinical studies, this is very typical of clinical studies. First shock efficacies around 90% with transvenous lead systems, even though we think they should be 100%, it's typically around, just around this number, which is how we came up with the predicted number for our clinical studies.

Again, what I think is more important even than the acute testing is spontaneous episodes, and the totality of spontaneous episodes where we wanted to evaluate included not just the IDE study, but we have additional data from non-IDE studies and from commercial evaluation in more and more patients which would allow us to have more confidence since we were not able to achieve the goal of chronic testing, the number of the patients we had -- that the FDA had asked us to get at the chronic testing. I think the fact that the chronic testing number was low was a reflection that in clinical practice, we just don't do chronic testing anymore because we're so comfortable with data when it's successful acutely compared to chronic testing.

It's just hard to get patients to do something that's gone out of favor for years now in clinical work, but again if we look at the patients, the discrete patients who had spontaneous events, again our success rate was extremely high. The only one that was deemed "not a success" spontaneously terminated. So we didn't get the chance to give another shock to see if that would be successful. So, again, there's no signs that this device has failures of spontaneous events and, you know, it far exceeded any of the OPC estimates that we had.

And then finally the question of any of the patients who missed the 65 J shock at implant, fortunately or unfortunately, none of them had a spontaneous event. So we don't have a enumerator or denominator, it's 0 to 0 essentially, to know how those patients did with their devices in place, but most of them, and I had -- one of the patients was actually my own who at 65 J, we got them at implant, we missed at 65 J at the chronic conversion but got them at 80 J, and discussion with the patient was I'd much rather keep this device in. I know it worked at 80 J, and transition to a transvenous device or start moving the leads -- and I think that was the general consensus at most centers. People liked the device. No evidence that there's any -- again, no signal that there's any evidence the device is going to fail chronically either with acute testing or by spontaneous events. Thank you.

MR. MARCOVECCHIO: The next question was a specific question from Dr. Lange this morning regarding reports of oversensing due to electrical equipment, and Dr. Burke will address what those sources were.

DR. BURKE: So two patients actually were identified to have had oversensing due to electromagnetic interference in the public purview. One exhibited oversensing when the subject was lying on a high voltage power line and --

DR. LANGE: I didn't see that in the user manual by the way; you shouldn't be doing that.

DR. BURKE: Actually, we have adjusted the -- not the user manual, but the patient manual so that they no longer do that, and actually counseling of the patient, and I don't think we needed to counsel the patient, actually led to this never happening again. I didn't personally interview the man, but he's very shocking.

So the other thing is that the second patient was leaning across the truck battery while changing a sparkplug in an over 90˚ heat and actually also developed electromagnetic interference and was inappropriately shocked for that, and once again, the patient manual or the patient has been counseled on this, and this has no longer occurred, and there was no recurrence of this in that particular patient as well.

I'll hand it back over to Mr. Marcovecchio.

DR. LASKEY: On this subject or a different one -- will phones?

DR. BURKE: Yeah, mobile phone, which is the next question, essentially this is in the manual, and it's taken off the standards that every device company utilizes; this 6" rule is essentially built off of a very large database of electromagnetic interference data and interactions in the public with ICDs, and we have not swayed from that one iota. In this particular device, it's recommended that you keep the cell phone antenna 6" away from the device so you do not get any type of interference, and in this, it's in the labeling, and it's also part of the manual for not only patients but also for physicians.

MR. MARCOVECCHIO: The next question I'd like to address was regarding some questions that came up this morning pertaining to leads. I'd like to start by just providing a bit more information regarding the testing that Cameron Health performed on the leads and then invite Dr. Gold and Dr. Burke to comment on it a bit more from a clinical perspective.

From an engineering perspective, we acknowledge this is a new device, and long-term data is yet to come in front of us. However, extensive testing was performed. The lead went through a variety of robust tests, and I'd like to clarify that the seven years that was discussed this morning was not intended to be a maximum duration of the lead's longevity, but as FDA mentioned, it really was a minimum design requirement which we tested beyond. When designing the product, we had to establish a minimum design requirement, and then we test to ensure that the device with bench testing data will give us confidence that it will last at least that long. It's by no means designed or expected to stop functioning as soon as we reach the seven-year point.

As shown on the screen here, if I can get this slide up, this is a summary of some of the specific testing at a high level that Cameron Health performed. You can see that a variety of tests were used, many of them common to transvenous leads and some of them supplementary. Cyclic flexural stresses were tested at 10, 45, and 90˚ which addresses one of the comments that someone asked this morning about the specific angles that were tested. The cyclic fatigue occurred at 10 times the expected flex strain that we would envision the electrode to experience in the body. Cyclic transaxial compression testing was also evaluated across the electrode body as well as tensile strength.

Additionally, the biostability of the materials was extensively examined, and the long-term shock capability, the ability of the electrode to deliver the number of shocks over its expected life was also evaluated.

So there was a wide range of tests which were submitted to FDA for their review.

At this point, I'd like to ask Dr. Gold to comment on the same general question more from a clinical perspective.

DR. GOLD: Well, certainly transvenous leads are traditionally felt to be the weak link in ICD systems. They're the leading cause of complications associated with transvenous ICDs. This was the major impetus for the development of the S-ICD to avoid the complications and the need to place a lead inside the heart.

Certainly this lead will eliminate the change of any intravascular damage even if the electrode eventually needs explanation. For whatever reason, you're still not going into the bloodstream for that.

Interesting, there's now been, as I think we mentioned earlier, almost 1200 S-ICDs implanted clinically. There's only been one electrode, one lead failure in all those 1200, and that was a lead that was cut by a scalpel inadvertently by the implanter. Fortunately, it was not of my fellows. But there's essentially been no non-iatrogenic failures of this lead to date over time.

There's an EFFORTLESS registry of 222 patients and now has a mean follow-up of over 9 months, and patients as long as 2.4 years, again with 0 failures noted.

And there has been chronic canine studies which are typically done going out to almost three years, which shows no degradation or no damage to the leads when testing the leads were performed at the end of that.

So, again, this seven-year is sort of a minimum expected, you know, based on design, but whether this will last 7.1 years or 70 years, obviously we don't know for sure, but it's been very, very robust in clinical studies.

DR. BURKE: So the final part of that question had to do with removal of this particular lead system, and since I'm an extractor, and since none of these leads are made out of diamonds, and they're all made out of substances that actually have permeability and don't last forever, as an extractor they've asked me to come up and just discuss a little bit about the removal, and I can tell you that I take out more leads now than I put in transvenously, and the reason for that is because of the weak link and constant flex fatigue of the lead systems in the transvenous space and across the myocardium where you're just having so many beats per month and per year, that it can't withstand that.

In this particular device system, it's sitting in a position that has very little flex fatigue, and that's a nice feature for the longevity, and then it also because it doesn't have to take so many turns and bends and have to be so flexible at the implant technique, you can actually have a position that's very stable and a durability on the lead system that's very nice.

As far as taking it out, I would much rather take this lead out than -- I think anybody who implants them would be happy to take this lead out than a transvenous lead. As an extractor, I'm pretty much taken myself out of business with this particular lead system because they won't have to be sent to a specialized center to be extracted. It's subject to far less biomechanical motion than is a transvenous lead, and the leads are exposed to the mechanical loading of every cardiac contraction as well, and the device is very well set up for robust survivability, and the core being not hollow allows for removability in a very much simpler fashion, and to actually re-implant in the same plane and within the same position would not be very difficult at all.

DR. LASKEY: So, Dr. Somberg to this point has a follow-up question.

MR. MARCOVECCHIO: Certainly.

DR. SOMBERG: With that said, then what is the Sponsor's recommendation in terms of the lead? I take it it's not going to be recommended that seven years, that's the minimum you say. So is there a test you can do? Are you studying that? I mean what? You're just going to wait until it fails. I don't think that's acceptable.

MR. MARCOVECCHIO: Sure.

DR. SOMBERG: So what do you plan to do?

MR. MARCOVECCHIO: The S-ICD System does have the ability to measure the impedance of the lead, which is an important indicator of the lead integrity. It actually measures the lead automatically when shocks are delivered. Dr. Gold would also like to address your comment as well.

DR. GOLD: I think the standard for all these transvenous leads is we measure impedance because that shows if there's any electrical discontinuity or an electrical problem, either a fracture where impedance gets very high, or a short where the impedance gets very low, or we see oversensing. So we see either shocks from noise with leads or non-sustained events with leads which gets monitored. So, in fact, this lead is identical, if you will, to other transvenous leads in terms of the way that we can monitor them, that we measure impedance weekly and can measure it as needed and that we can measure for inappropriate sensing. So it's really no different.

There are some more advanced monitors that are put into some ICD systems because of high rates of lead failures in some of those leads, but the principles are essentially the same, look for oversensing, looking for impedance changes, and this system does it just like any other system. So, yes, it will continue to be monitored, and obviously it gets tested more rigorously at the time of pulse generator replacement, but even transvenous leads that may have a 30% failure rate at 5 or 6 years, some of them are in there at 15 years, and we just continue to monitor them until we see a problem. We don't pull them out at any point to replace them at any point electively.

MR. MARCOVECCHIO: Those were all of the questions that we captured. So I thank the Panel for the opportunity to address them.

DR. LASKEY: So one other, device, adjunctive device about MRIs.

MR. MARCOVECCHIO: We have not tested this device to be compatible with MRI diagnostic testing, and the labeling clearly indicates that accordingly, similarly to a majority of other implantable devices which are not tested to be compatible with MRI. Thank you.

DR. LASKEY: Thank you.

DR. LANGE: Just a follow-up, just a clarification. So, again, just to clarify because at one point someone said the user's manual had been changed and someone said we would change it, and the user manual we have, I think it's Exhibit 6 or 7, Exhibit 7, does not have some of that material regarding larger prep size or EKG screening analysis change or of a dual zone chamber. So if the FDA requested that, my assumption is that the Sponsor would be willing to do that or is in the process of.

MR. MARCOVECCHIO: Your assumption is correct.

DR. LANGE: Okay.

DR. LASKEY: At this point, I'd like to give the Agency an opportunity to respond to this morning's queries. There was a question for the engineer about -- did you have more information for us about the lead, its construction or its integrity or anything to follow on?

MS. CUTTS: My name is Erin Cutts. I'm the Engineering Reviewer for the lead, and I did put my descriptions on a slide I think, which I'm not exactly sure how to get that up there.

So you've seen this picture before, but I just put it up there since we were talking about the lead, so we know where the different areas are. There's the connector and then the sensing electrode, the defibrillation coil and the distal sensing electrode. I was just going to go through the visuals I have, and if you have any questions, I'm happy to answer them.

And then the cross-section of the lead. So the blue cables are for the defibrillation coil to terminate at the proximal and distal end of that coil, and then the red is for proximal sensing electrode, and then the center cable is for the distal sensing electrode.

I'm not sure if this is too detailed for what the Panel's requesting, as far as what the lead looks like on the testing or anything, but I'm happy to talk about the materials for the lead as well. Is that something the Panel is interested in? Is that a little too detailed?

DR. LASKEY: Too much information.

MS. CUTTS: Okay. I thought so.

DR. LASKEY: But one question --

MS. CUTTS: Yes.

DR. LASKEY: -- as a non-electrophysiologist. I heard the word hollow bore this morning for the standard ICD as opposed to --

MS. CUTTS: Right. So most intravenous leads use a stylet or some sort of -- something down the middle to straighten the lead out while you're putting it in. So you don't use a stylet with this lead. So you don't have a hollow lumen. That's essentially that question.

DR. LASKEY: Okay. So in the interest of information overload, since we need to be robust for the rest of this, were there any other detailed engineering level questions? No. Then thank you.

And I'll move on to Dr. Shein. Did you want to respond on behalf of the Agency to this morning's queries?

MR. SHEIN: Mitchell Shein, Branch Chief of PDLB. I think that what you saw this morning were two very consistent presentations between both sides of the aisle. It's nice in Washington to get some concurrence on opposite sides occasionally. I don't think we have a whole lot of comments.

One thing I would ask you in your deliberations this afternoon, though, is as we're now going through the labeling, sitting on the sidelines, we've noticed that there is no requirement per se for induction testing at the time of implant, and I'd ask that the Panel weigh in when we discuss the labeling questions, whether you think that's necessary or appropriate. Right now I believe the language is that it's at the discretion of the clinician, which might be the practice with ICDs, but I don't know that if that's necessarily or if you would consider it appropriate for this S-ICD System.

DR. LASKEY: All right. Thank you. So at this point, I'd like to move on in terms of the Panel Deliberation portion to give us, the Panel, another 30 minutes to address the Sponsor or the Agency about uncovered, untouched, or still troublesome queries related to the morning presentations. So I'll throw the floor open to -- Dr. Lange, you had a query?

DR. LANGE: Just a question of the Sponsor, again just a clarification. I know that the device is prepared to deliver five shocks for each episode. The question is, is it the same polarity? I mean is it the same -- obviously it's 80 J. Is it the same polarity, or does that switch after two or three shocks if they're unsuccessful?

MR. MARCOVECCHIO: The device automatically switches polarity if the first shock is unsuccessful, and it remembers the last successful polarity and uses that same successful polarity if a subsequent episode were to occur.

DR. LANGE: Thank you.

DR. SOMBERG: John Somberg. This is to the Sponsor. I thought the FDA's discussion of the proposed study was quite good, the postmarketing study, and I wondered if the Sponsor is considering adopting their suggestions or filling in when they question, and specifically I'll say, one is to, are you reconsidering the performance goal of the efficacy? Are you going to look at adversities? Are you going to, you know, adverse events, et cetera, and are you going to develop sort of a monitoring program to be able to obtain that data especially in light of the Social Security problem, which I didn't know about until I looked at this Panel pack, and it's just another thing to object to in life.

MR. MARCOVECCHIO: Thank you.

DR. SOMBERG: You're welcome.

MR. MARCOVECCHIO: I'd like to address some of those comments. One of the most important comments I'd like to make is, and I think the Sponsor will take responsibility for not being clear, our intent with the endpoint was actually to measure what's more akin in the IDE study to the Type I, II, and III complications. We should have done a better job of clearly explaining that. We agree that those would be important types of events to gain understanding throughout the post-approval study duration. So I'd like to clarify that point. So that addresses one of them.

With regard to effectiveness, we already indicated that we do agree that effectiveness is also important to continue to assess during the post-approval study, and we plan to put a mechanism in place so that we can capture spontaneous episodes, which are the most intuitive and important measure of effectiveness for this particular product.

Was there another element that I haven't addressed, or was that it?

DR. SOMBERG: I think the performance goal also. As you extend the duration, let's go below 79%. I don't think -- everyone on the

Panel wince at a performance of below 79.

MR. MARCOVECCHIO: Sure. Thank you for reminding me of that. With regard to the performance goal, the intent was to derive a performance goal based on the learning from the IDE study. We did not specifically articulate the exact number yet because we need a bit more time to think about that, and we're committed to working interactively.

The adjustment that was referred to also could have been better communicated by us. The adjustment was intended to point out that if we only have data to six months or one year in the IDE study, but we're going to design an endpoint beyond that, that we would have to think about the appropriate way to adjust for the additional increased time where it's reasonable to expect that an additional amount of clinical events might occur, and we are again committed to working with FDA to doing that in a manner that's appropriate.

DR. LASKEY: Ralph.

DR. BRINDIS: Ralph Brindis. Two questions. I think the Panel's going to be asked to give our thoughts about subgroups that may not be suitable for the device, and I was wondering if the Sponsor could give some insight about how you would handle -- what your recommendations to people who have had chest radiation or other types of chest surgeries that might put them at anatomic disadvantage for risk of infection.

MR. MARCOVECCHIO: I'm going to ask Dr. Burke to address that clinically oriented question.

DR. BURKE: Yeah, I think the specific issue of radiation to the chest was not looked at. None of the patients would be identified in the IDE study as having had radiation to the chest.

That being said, the surgical -- the chest surgical patient population was quite robust and I think tells you the story that we can actually have a very good result with very little variation in somebody that's had prior chest surgery.

Secondly, I actually had a patient in the cohort who, and this would be another question that would come up, is what do you do when somebody has not had chest surgery, but then has the device and then basically ends up having to have a sternotomy, and in this case, it was beautiful. The patient underwent a successful revascularization after a three-vessel coronary was identified. Actually, the man developed left main disease over the timeframe. He was one of the early implants and, about two years into it, developed left main disease, underwent open heart surgery, had a sternotomy right next to the lead. We were very interested to see how this lead would react, and in actuality, the patient received an appropriate shock during his hospitalization in the first four days postoperatively, and actually the lead system and the device functioned beautifully, and also the impedances throughout his hospital and now in follow-up have been quite robust and good.

So I think I feel comfortable as an implanter with a wide variety of patients that receive this device, that actually it's very well set regardless of the clinical circumstances, and it's just a matter of knowing where it's at and being careful and knowing that it's a new lead system there.

DR. BRINDIS: I have a follow-up question that is suspect you'll be the one answering it, and I apologize for keep on perseverating on the issue of the mean of permanent pacemakers, and I understand in the study, none were needed. You have a younger population. I am not an electrophysiologist, but I would be interested in an electrophysiologist's feeling. Do you have any reasonable predictors related to surface electrocardiograms in the elderly who might end up being a huge population for you that we could somewhat predict a relative risk going on for permanent pacing that would lead a clinical electrophysiologist to make different decisions about which device to use transvenous versus subcutaneous?

DR. BURKE: When we started out with this particular protocol and discussing it at the University of Chicago, we did bring this up as to how are we going to actually identify these patients, and we actually fell back to the literature from when there was no pacing with ICDs, and when you look at the patient population that had both systems, at our institution in the early to mid '90s, it accounted for 6% of the population that actually had both devices, and when we're looking at the issue of bradycardia, I think that there isn't really a predictor in terms of sick sinus syndrome. We certainly have -- I have patients that have bifascicular block that are in the IDE study and have not progressed to meeting permanent pacing.

And then there's data historically looking at bifascicular block and saying it's about 11% in a lifetime that end up developing high grade AV block, and so I think from that perspective it's a process that moves on over time, and it's something that you have to deal with, but in this particular case, you can actually add in a bipolar permanent pacemaker with a lead system that's more robust, less prone to fracture, and is smaller in the intravascular space, and it's quite enticing to think of that as a possibility should, over a long period of time, the patient needs permanent pacing.

I'd like to bring up Dr. Gold just to highlight a few points.

DR. GOLD: Yeah, I just wanted to reiterate a couple of points. There actually is pretty good historical data from single chamber ICD studies, SCD-HeFT probably being the biggest one, but we had other studies before that, that the incidence of upgrades or requirements for pacemakers in those studies is vanishingly small, on the order of a couple of percent. So we don't see 10, 15, 20% of patients who get single chamber ICDs from AVID, from SCD-HeFT, so on and so forth, going on to require pacemaker implantation. If you do require pacemaker implantation, there's no contraindications to putting in a pacemaker in a study. There's lots of data now, that the electrophysiologists on the Panel I'm sure are well aware of, that dual chamber pacemakers to start with are fraught with potential problems and actually have higher complication rates and high problems. So the idea of a anticipatory response of putting in a dual chamber ICD is probably not a good strategy and I think, I just saw something on the internet, yet another study showing dual chamber ICDs are not a good thing to do unless the patient truly needs that. If they truly need pacing at the time of implant, they should not get this device.

The bigger category which we haven't touched upon is the CRT group. So, again, if a patient needs cardiac resynchronization therapy, don't put this device in. I mean put in a proper CRT device. If they need dual chamber pacing for true clinical indications, don't put in this device. Put in a dual chamber ICD, and we're talking, you know, probably around 50% or so of the population might fall into one of those two groups of patients, but for patients who require single chamber ICDs, multiple studies with much longer follow-up than this have shown very low rates of having to upgrade in those studies. In this study, it would just be implanting a pacemaker.

I don't know if Dr. Burke may have some final comments.

DR. BURKE: No.

DR. LASKEY: Dr. Gold, you may want to stay there because there was one more question about pacing capabilities.

DR. KARASIK: Right. So I just wanted to clarify something.

The post-shock pacing capability is a programmable feature on/off. If you turn it on, it only provides pacing in the post-shock setting.

DR. GOLD: And only up to 30 seconds.

DR. KARASIK: And how do you test the ability to capture the heart?

DR. GOLD: That was monitored at the time of the induction testing.

DR. KARASIK: So you did an induction with the post-shock on afterwards?

DR. GOLD: Right. So post-shock testing was turned on at the time of all induction testing, at the time of implant, to test that, and what we -- we then monitored the patients to see if it was appropriate in terms of did it capture if they got bradycardia and did it not capture.

DR. KARASIK: Is it VVI or VVO shock?

DR. GOLD: VVI.

DR. KARASIK: VVI. So let me just -- I'm sorry. So unlike traditional leads then, you would not check pacing at the time of implant, just connecting to a PSA and --

DR. GOLD: Right.

DR. KARASIK: -- testing for capture.

DR. GOLD: It's transthoracic. It's high output transthoracic pacing. So it's not meant to provide standard bradycardic support --

DR. KARASIK: Correct.

DR. GOLD: -- but to prevent those long pauses that we occasionally but rarely see, you know, in patients following a shock to terminate a ventricular arrhythmia.

DR. KARASIK: And it works?

DR. GOLD: And it works, yeah. It works surprisingly well.

DR. KARASIK: Okay.

DR. LASKEY: I have a Dr. Somberg question and then a Dr. Kelly question.

DR. SOMBERG: Dr. Gold, don't sit down. You know, we all need a little exercise after lunch, but I'm not sure --

DR. GOLD: I'm trying to avoid a DVT here.

DR. SOMBERG: Standing is best. I just for a moment touched on the rationale for 30 seconds when I saw that because when I noticed that, in reading the packet, I was trying to think of why exactly 30 seconds. It's rare to have bradycardia, but when it does, is it always less than 30 seconds? Do you have any literature on that?

DR. GOLD: That's a good question. I am not -- if I quoted the literature, I'd probably be making it up. I think, at least my clinical experience, is that when you do see a pause, it's a short pause, maybe 3, 4, 5 seconds, and everyone gets nervous. I mean maybe you see 10 seconds. I'm not aware of, you know, cases of patients being asystolic or just never beat again after a defibrillator shock. So I think 30 seconds in my mind is well beyond the boundary of where you'd see a pause, of where you'd see bradycardia following an ICD shock, and I see some of the electrophysiologists on the Panel all clustered over here, sort of shaking in agreement. I just don't think that's been much of a problem other than short pauses, but I personally am not aware of literature on the duration of pauses or asystole following defibrillator shocks. I don't know. Dr. Burke may want to answer it.

DR. BURKE: Yeah, actually if you look at SCD-HeFT, which was a single lead non-pacing type of interaction of the transvenous ICD system and spontaneous events versus induced events, you're more likely not to see post-shock pacing in the spontaneous event, and it was less than 2% requiring any for less than four beats. It was more likely to be seen in induced events because you're undergoing anesthesia and you have either general anesthesia or conscious sedation, and so that actually created a higher, but there was no one in the IDE study that actually required pacing for more than a few seconds.

DR. KELLY: I just had a question about the number of shocks. So we heard that the device at implant is good for 100 shocks, and then from the FDA we heard that if it lasts 5 years, it's good for 21 approximately. So my question is do you have any idea how that curve works? Like if someone's had a device for three years, do we have any idea about how many shocks it could deliver? And the reason for the question is that you had a primarily primary prevention cohort, and they have a much lower incidence of VT storm, but for secondary prevention, it's up to 20, 28%. So I'm just wondering if someone's had a device for three years, how many shocks can you expect it to be good for?

MR. MARCOVECCHIO: Sure. As we discussed, and I think everyone understands, the relationship between the number of shocks and longevity are a function of one another. The latter part of your question is a bit more clinically oriented. I'd like to ask Dr. Gold to address it.

DR. GOLD: Yeah, there's actually been some modeling done based on, in the literature and one of the most recently released devices is, in fact, the Medtronic Protecta device, single chamber device, compared to the S-ICD here, and based on at least available, the published data from them in the manuals, if we look, the single chamber ICD does have a slightly higher, you know, probably close to a year longer longevity at implant, but based on the number of full energy charges per year, and again, just for those of you not used to device, the device is the capacitors get charged and then discharge routinely to sort of exercise, if you will, the capacitors so that they'll be able to charge rapidly, and that's typically around three or so per year for most devices, every four months or so, but if a patient gets a shock, it then restarts the clock of when you need to re-exercise those capacitors, but as you can see here, that if we were all the way out to eight shocks or eight capacitor charges per year, which may or may not be total shocks, the curves actually start to cross. So all devices have the same impact essentially, that the number of charges will reduce battery longevity. The longevity of this will be very similar to a single chamber transvenous device once you get out to about six or so charges per year, and even out at eight charges per year, you know, we're still talking about device longevity only going down to about four years or so from about five years. So we're not talking about -- obviously if you get 80 shocks from a VT storm, that's going to deplete any battery of any system, but it's relatively minor, you know, not to the patient maybe, but we're losing a year if they were having eight shocks per year over the four year period.

DR. KELLY: Okay. Thanks. And one more quick question. The charge times, you know, they're a little long in some cases. Do you have any data on how many people had syncope before shocks when they had them spontaneously?

DR. GOLD: I'd rather have someone else -- I think Dr. Burke has the IDE data.

DR. BURKE: For the spontaneous episodes in the 16 patients, there were no reported episodes of syncope for the spontaneous episodes. Obviously the patient who was in storm was in, the two patients that had storm were in some extremis, but they were intermittently taken care of in a gurney. So it was not specifically reported that there was any syncope associated with any of them.

DR. LASKEY: Dr. Lange.

DR. LANGE: Question regarding the dual versus single zone discharge. You obviously decrease the amount of inappropriate discharge by going to dual zone, basically going to dual zone therapy. I guess my question is related -- would it make sense to force everybody to go to dual zone, or why not have this discriminatory capability with the single zone? In other words, what you're doing is you're measuring QRS morphology or slew rate during that time period, and why not just force that.

MR. MARCOVECCHIO: Yeah, you effectively asked what circumstances might exist where single zone would be more appropriate for a patient than dual zone considering that we saw some reduction in inappropriate shocks. I'd like to ask Dr. Gold to address those clinical circumstances.

DR. GOLD: Certainly I think it varies from practice to practice. We used to use single zone programming much more frequently with transvenous systems in a lot of patients, and I think the data from the transvenous world actually taught us first that dual zone programming and allowing discrimination up to faster rates was a better idea, and we're going more and more.

Personally, I turn on dual zones in almost all of my transvenous systems to allow us to do that. That allows us to have discrimination there. What we learned from this study is that the same thing works, that if we allow it up to -- you know, if we allow it, it can be more effective.

The question I think all of us have some uncomfortable -- because there is no data, that when we get up to rates, very, very high, 250, 270, 290 beats a minute, those rates, what would happen with dual zone programming? Would it further delay therapy? Would it be fooled by some of these rhythms? And it's essentially no data looking at it there. So for that reason, it's always been programmable, and all devices have a rate above which it becomes a rate only device. When you get too fast, you don't want to start messing around or risk that you're not give therapy for that because you get into rates where the chance of that being a supraventricular arrhythmia is exceedingly low at 300 beats a minute, whereas the chance of it being a ventricular arrhythmia that you would never want to miss is going to be exceedingly high. So all devices have the capability of having a "VF zone" which we use in transvenous systems and with this as well.

So I'm not sure that we want to just make the discrimination to infinity for a device given that there are no data for that, but certainly in a vast majority of my patients, I would use dual zone pacing, dual zone discrimination.

DR. LANGE: But there's no case where that would be single, where there's an indication just for single zone?

DR. GOLD: There are certainly some people out there, you know, who use very high rates. So for some of their young patients, they may set their devices at 200 or 220 beats a minute and will use it in a single zone. So they're only protecting against ventricular fibrillation who feel that again, we're getting towards the rates where dual zone may not be useful. It's not my style of programming but, you know, we all have our own sort of nuances and idiosyncrasies of how we program devices but, you know, if one was going to take a patient and only give therapy at 220 beats a minute, you could argue that dual zone programming may not be needed or may not be a good idea at that point. So we certainly could construct scenarios which is why I think probably most reasonably all devices have the option of single versus dual zone, and it's sort of how you'd recommend in terms that they be programmed, which has certainly been an evolving area the last few years in electrophysiology research.

DR. LASKEY: Dr. Milan.

DR. MILAN: I have a question about how the devices were programmed when the patients left the hospital. So we heard a little bit about the breakdown of single zone versus dual zone, but what are the rate cutoffs? Do you have data on that?

MR. MARCOVECCHIO: I don't have that data at my fingertips. I can tell you that the protocol itself did not prescribe a specific setting. It was left to the discretion of the investigators.

DR. MILAN: If you have that data, it would be useful to me, and the reason why I'm curious about it is because while the protocol didn't prospectively specify programming the device in the chronic setting, it did specify the VF cutoff zone during testing, and I'm a little bit perplexed by that because that's not what we would do with the transvenous device. With the transvenous device, we would program it to the settings that we're going to leave the patient in chronically, and then we would test it to see if at those settings it can detect ventricular fibrillation adequately, and then that's it. That's a wrap. In fact, what we commonly do is even make the settings less sensitive for at least one of the tests to make sure that even under sort of a penalty of a less sensitive setting, the device is still capable of detecting VF.

MR. MARCOVECCHIO: Sure.

DR. MILAN: I'd like to see the data that you have.

MR. MARCOVECCHIO: Okay. I'd also like to invite Dr. Burke to comment on the point you raised.

DR. BURKE: Yeah, maybe I can give you a perspective of how configurations were programmed, and you can see in this slide, that in the first third of implants, single zone was the majority, and that in the second third, dual zone became the majority after the compelling investigator meeting which described the benefits, regardless of what the cutoff rate was for the shock zone only, in having a dual zone because it allows you to track the dynamic morphologic changes that are occurring as your heart rate gets higher.

And I think that the concept here of inappropriate shock benefit and preventing inappropriate shocks is really compelling to actually put a dual zone on regardless of the cutoff, and I can tell you, have 12% of the patient population in the IDE trial, that we did things much differently in this particular trial in terms of your experience with transvenous. We would have cutoff rates in the shock zone of 250 beats per minute, which would be very rare to have a VF-only zone at 250 in a transvenous ICD lead system, but in this particular case, with the sensing algorithm, we felt very strongly that with the conditional zone set at 200 and the shock zone set at 250, and this was in a majority of the -- you see, there are younger patients. So you want to be very careful about this, and so the concept was that it was usually set higher on average in the IDE trial, and certainly at our institution, we were above 220 as the shock only zone, and we, after the investigator meeting, put on the dual zone, and that was the variable thing. That would depend on the patient's age and the clinical circumstances, that you would have it at 170 to 220, 170 to 250, depending on the patient's condition.

DR. MILAN: Just in follow-up, I mean what I'm getting at is the tradeoff that exists, right. I mean what you want to do is you want to be highly specific so that you only shock ventricular arrhythmias, but you also want to be 100% sensitive so you never miss a VF episode.

DR. BURKE: Right.

DR. MILAN: And when you lower the VF detection rate, then you're going to become more sensitive and you're going to sacrifice unspecificity perhaps, and what I'm trying to understand is --

DR. BURKE: Yeah, let me --

DR. MILAN: -- you had some issues in your protocol where there were some excessively long time to therapy, and that was due to sensing presumably, I mean by your own explanation, and so this long tail that exists, I'm concerned about how long that tail might be if the VF zone during testing, which is where this long tail was observed, how much longer does that get when the VF zone is increased from 170 to 190 or 200 or --

DR. BURKE: Right.

DR. MILAN: That's what I'm driving at, and that's why I want to see how these devices were programmed as the patients left the hospital.

DR. BURKE: Yeah, and so the issue of sensitivity has not been an issue at all. I demonstrated that with detection sensitivity, and certainly with the spontaneous events, that was not changed.

And the second thing is that the specificity I think is demonstrated to be markedly increased with the dual zone, and so you don't lose any sensitivity by putting a dual zone on. You increase in specificity, and I think that's been the key feature to the whole thing.

But let me bring up Dr. Gold because we did a head-to-head-study looking at -- I think this might help, and Dr. Gold's published a paper recently looking at head-to-head comparisons of transvenous versus subcu testing for arrhythmias.

DR. GOLD: Actually it was a great question because the timing's perfect. In this month's issue of *Journal of Cardiovascular Electrophysiology*, we've just published, where I was the lead author, of a study called START, which was a head-to-head comparison of different defibrillation algorithms from implantable and the Cameron algorithm, and what we did in this study was to, at the time of implant, collect arrhythmias, both supraventricular arrhythmias, atrial fibrillation, supraventricular tachyarrhythmia, as well as ventricular fibrillation and ventricular tachycardia. We then put them on a tape recorder and then offline played the identical rhythms through everybody's devices set at their nominal ways of discriminating, but we set the zones at 170 beats a minute to discrimination, all the way up to 250. So the shock only zone became 250 beats a minute, which is the worst-case scenario that we were talking about here.

If we can pull up the next slide here. If we actually look at the performance of this, we can see with regard to -- this is the specificity data. I'll show the sensitivity data next, but with regard to specificity, what was interesting is that the Cameron Health, the S-ICD had 98% specificity meaning that 98% of the time it appropriately withheld therapy for a supraventricular arrhythmia between 170 and 250 beats a minute, and compared to the three major transvenous systems here, and I don't want to go through, you know, comparing them because that's really not the purpose here, but they all had lower specificities for the identical rhythms played through these devices, and it didn't make a difference if they were in single chamber mode or dual chamber mode, which I think is another lesson we've learned over the years, that dual chamber sensing as opposed to dual zone sensing does not really improve your specificity. So the Subcutaneous-ICD had the best sensing algorithm. So I think it's part of the ultra far-field electrogram which you can see from that, but I think the reassuring aspect for all devices is that if we look at sensitivity now -- so this is now for ventricular fibrillation or very rapid ventricular tachycardias -- essentially nobody missed. There was minor episode that missed. So you can turn on dual zone sensing to withhold shocks for SVT all the way up to 250 beats a minute, yet you're not going to miss any ventricular fibrillation episodes, and this is as high as I think any device can be programmed to my knowledge and as high as any study has ever tested it, which is why we don't go to infinity.

DR. MILAN: So help me out with this because I'm trying to get to the same place where everybody else seems to be, that there's a high degree of confidence in the sensitivity of this device. When we look at the time to treatment, the time to delivery of therapy in the VF induced episodes, and during testing, you know, 88% of the patients got therapy in less 18 seconds, which means 12% got, you know, it took more than 18 seconds to deliver therapy. You know, with 1.2% of the patients' time to delivery greater than 24 seconds, that happened with the transvenous system. I mean the charge time is about 10 seconds at implant. So that means 14 seconds to diagnose VF. If that happened with one of my transvenous systems, I'd be doing a lead revision. That would not be clinically acceptable for me to send a patient home with that. So I'm just trying to get to the same place where you seem to be, that there's this high degree of trust and confidence that this thing is capable of reliably sensing VF.

DR. GOLD: That's my name. You remembered. Thank you.

So, in fact, you know, you point out correctly that there is a small percentage of patients who are at the sort of tail here of longer detection periods. I should point out that with induction testing, there's a two second blanking period in the device. So after you induce, because of the induction method which can saturate the amplifier, the amplifier is closer here to two seconds, when we look at that, and then the time to therapy certainly was variable. There's some variability in battery chart times, to get up to the energies, and there's also -- there clearly is some undersensing at times, and again as I'm sure you've experienced as well, not all VFs are the same. They may not all look the same. Some of them have very small signals for a while and they get a little bigger, and all devices will have periods where they may slow or start to under-detect and then redetect again, but there was no episodes in which the system did not detect, did not charge, did not deliver, and essentially, you know, were able to terminate at some point all of these differences, you know, and what we find is that there were no clinical events noted that despite these long charge times or long detection to therapy times, there were no untoward clinical events with this, and there was variable response times which was not due to very long detection rates for the devices.

If we look at, you know, if we look at comparisons with the literature for different ventricular rates and different devices that are out there, we can see that some of these are slight outliers, but detection time for commercial devices take some time, too, particularly for ventricular fibrillation because a little bit of undersensing and in charging is not all that unusual.

So while I think it is certainly a little bit longer than what we see with transvenous lead systems, we could not find again any evidence that patients were having syncope, that the patients were having untoward events. And I think the interesting thing that this fortuitously aligns with, even though it was developed years ago for other reasons, is that we're intentionally now programming our transvenous devices to wait and we're prolonging our detection time in transvenous devices because we learned that as battery technology got better, we were giving shocks too early, and studies of transvenous devices show that if you wait, many of these arrhythmias will spontaneously terminate both ventricular and supraventricular arrhythmias. So this is actually more in line with what we're doing with transvenous devices. I acknowledge a little bit longer, but more in line of how we program many of our transvenous devices to go out to 40 beats before they'll even start to charge, or 40 detected beats.

DR. LASKEY: Yeah, I think we've pretty well gone around this tree, and another way to paraphrase it is these small numeric differences pointed out by Dr. Milan don't appear to have any adverse clinical sequelae, and I think what this Panel ultimately will weigh in on are the heart events, the clinical events.

I would like to move onto Dr. Naftel and then give the other Panelists their final opportunity to query either the Sponsor or the FDA before we go into closed panel. Dave.

DR. NAFTEL: So I'm totally switching gears to the post-approval study. So first of all, I want to applaud you for using a registry because I understand that on occasion a registry can be useful in the regulatory process. So that's good.

So there are two extremes that I can see, and I'm real interested in how you're going to approach this. One, you could use the registry, the NCDR ICD Registry as is, and you add just a few more variables, but the registry is sort of guiding what happens and you're a little bit standoffish and the registry goes. That would be one extreme.

The other extreme is the registry becomes a data collection tool for you as you totally rebuild it with a lot more follow-up, more adverse events, and like I said, they become a tool that feeds you the data, but you do the monitoring, the informed consent, the auditing, and especially the data analysis.

So I can see totally two different extremes. I'm wondering, have you thought through all that, and which side are you leaning towards?

MR. MARCOVECCHIO: We have given some thought to that, and we do need to give additional thought to that. We believe that the registry collects the core information that provides important data on safety and effectiveness, and we also acknowledge that the registry doesn't collect some additional data that I think everyone would agree is important to continue to study. Therefore, we're going to put a supplementary mechanism in place to collect that data. We also agree that it will be important to do some active monitoring to ensure that there is no under-reporting. So we're leaning towards that, to address your question about which way we're leaning there.

I'm not sure if that specifically answers your question or not. Does that address your question?

DR. NAFTEL: Yes, I'm just curious how you've thought through it because it will take some thought and a lot of effort, but I think it's a great idea, and you've got a good basis, but like I think you're telling us, this Registry doesn't have everything you need. So there will have to be some additional programming and a lot of additional discussion.

MR. MARCOVECCHIO: Sure. I'd be happy to invite Dr. Kremers up to provides some additional commentary on that.

DR. KREMERS: Hello, Mark Kremers. You are correct. The ICD Registry is incomplete in terms of gathering the information that would be needed to track this device longitudinally. The registry is very good for acute implant complications, and in the premier centers, a title I did not choose, following device replacements, leads that require repeat surgery would also be tracked via that mechanism.

Things that are missing clearly would be episode data and infections that do not require antibiotic therapy.

So there is potentially a mechanism for using the registry to do so. There is precedence, is my understanding with working with a sponsor, to develop a specific tool that can be added onto the registry to track this information.

DR. LASKEY: And, Dave, I would suspect we're going to make some suggestions here within the next hour about what else to add, what we'd like to see.

Okay. Ralph.

DR. BRINDIS: Ralph Brindis. Actually I'm going to make a registry comment, in that the ICD Registry, and I'm sure Mark knows the data better than I do, is actually in the midst of participating in a five-year longitudinal study looking at efficacy in certain subgroups that were not officially looked at related to the initial CMS NCD coverage, and maybe Mark can comment on how it is going, but it has in place, adjudication related to use of device therapies. So it's not going to answer -- so we have an experience that we're actually ongoing with a five-year study. It doesn't have all the other variables that I suspect would be on the FDA's and the Panel's wish list, but we do have a precedent that's ongoing.

DR. LASKEY: I'm going to take advantage of this golden hiatus here to ask our other members to query either the Sponsor or the Agency before I move onto closed Panel. So, Ms. McCall.

MS. McCALL: No.

DR. LASKEY: No. Mr. Dubbs?

MR. DUBBS: No.

DR. LASKEY: Nobody. Great. All right. Well, thank you.

If no one has any other questions for Sponsor or Agency, I would like to close the Open Panel portion. I suggest in the interest of time that we go right to out internal Panel Deliberation following which we'll take a short break and then do the FDA questions.

So we now begin the portion of the meeting where we as a Panel will deliberate amongst ourselves. I'd like to open the floor to my colleagues and experts around the table to begin deliberating on any issues you may have with any of the data you've heard today, either this morning in the presentation or these most recent discussions. Dr. Somberg.

DR. SOMBERG: Well, I'll lead off by saying I was very impressed by the Sponsor's presentation, and I'm particularly reassured by some of the recent publication in *Cardiovascular Electrophysiology* by Dr. Gold where it looks, and granted it's in vitro work, but it looks like the device with this dual mode has very good sensitivity and specificity, and that is reassuring because in this early stage, we're always going to have smaller numbers, and it is very difficult stepping back from just the particular situation to the general; it is very difficult to introduce a new technology, a new device, in a field that has moved very rapidly and delivered excellent results. So competing with the transvenous systems is quite an accomplishment, but this device will I believe find an appropriate niche. A lot of the questions have been answered. There's need for additional implanter training. I believe it's going to be important for a patient manual, and that sort of thing. There's going to be need for a follow-up study.

But with all that said, we've had more information today than I've seen in multiple fields with devices presented at this formative launch stage. So I've been reassured especially with the device's sensitivity and specificity in competition with a very mature and very established competing, not sort of technologies, but competing mode of acquisition and delivery, transvenous versus transthoracic.

DR. LASKEY: Just for folks to continue to think about, and then Dave, we'll get to you. I'm sitting here re-reviewing the patient population here on the sample, and I do think that there are some differences between this study sample and the target population, that we should think about going forward in terms of what else we should be looking for and in whom, and which subgroups as Ralph has pointed out, but this is a group in which 40% of the population was younger than 50 years of age, and about a third had ejection fractions greater than 35%.

So it's clearly a much different group than we traditionally think of for ICDs, and I think as we go forward here and expand the "eligible" patient population, we're going to see a lot of different folks, and we need to just think broadly about what else we might want to be looking for. This is a "relatively healthier" group compared to the literature.

So that said, Dave.

DR. MILAN: So just to respond to Dr. Somberg's point about the sensitivity and specificity of the devices, that that admittedly ex vivo algorithm that Dr. Gold -- I mean I haven't seen all the details, like the time to diagnosis, for instance, which is a point that I'm concerned about for these devices, but also the setting. So if you set your VF zone at 170, it's easier to pick up VF. If there's a little bit of dropout, you still have a rate of 170 than if you set your VF zone or your detection zone at 200. This is why I think it's important to know how these patients were programmed as they left the hospital because the device was clearly specified to be tested with a VF cutoff zone of 170, but if later the patients were programmed to a detection zone of 200, we don't know that they have the same sensitivity of that higher cutoff rate. So you actually put your finger on the area that I actually have many of my greatest concerns.

And to Dr. Laskey's point, which is we should be driven by clinical endpoints, I agree. The issue with prolonged detection is one of syncope. There were no syncopes, but there were only 16 patients who had spontaneous events in this IDE study.

DR. LASKEY: Dr. Naftel.

DR. NAFTEL: I apologize for a very naive question, but I don't have any idea of how when there's an inappropriate shock, what does the patient feel and how disconcerting is it?

DR. SOMBERG: It's not fun. It hurts, and I'm the -- there are experts around the table who are more expert than I. I'm a passé electrophysiologist, more pharmacology put out of business by the engineering crews, but the big problem is passing out because it's one thing to get all these complaints and everything. It's another thing to pass out, and if you pass out, there's things you can't do. I mean you don't want to stand on a terrace. You don't want to wait for a train on the edge. You don't want to drive a car. You don't want to do 100 other things that passing out is immiscible with. So that's a major problem.

But, you know, going back generalizing a little bit more, there's a problem here. It's a formative technology. There's still a small number. You know, you have 16 patients involved. You're not going to make a definitive thing where you get a 1,000 shocks. This was mostly set on performance. Those are the agreements or the development set on performance. It's met everything that it's been demanded of so far, but it has to be expanded, and that's why the postmarketing, everyone agrees, is going to be so critical to obtain that information, and to do that -- because I don't think we're so worried about inappropriate shock if it just hurts. You know, it's unfortunate, but that's the way it is. But it's inappropriate shock that someone passes out. It makes it more difficult to shock again. So the longer you wait, the harder it is to get out, and you only have a certain number of shocks in this machine. So those are the problems, and you're going to have to test that out in real-life situation.

DR. LASKEY: Ralph, we're not ending this meeting at 3:00. So do you have any?

DR. BRINDIS: Just to make sure I understand your request here, you'd like us to make some general comments at this point related to the device.

DR. LASKEY: Or things which are still somewhat disconcerting. So Dr. Milan has spoken articulately to this SNS aspect of this, but things we should use in our thinking for answering questions and making recommendations. So what still bothers you?

DR. BRINDIS: The device itself does not particularly bother me. I am interested in potentially having further discussion exactly what we would -- data we would end up collecting in the post-approval study, how in depth we would want information.

Oftentimes with post-approval studies, at least as I'm in my learning curve, we're looking at issues of safety and efficacy, but there may be other issues related to battery length and other things that have come before that might be of interest, and again, the question is how much we're going to make demands upon the Sponsor if the FDA decides to approve the device and decides to have a post-approval study in terms of the cost involved and how much data to collect. So I think that's been pretty vague actually as to what would actually be covered in a post-approval study.

DR. LASKEY: And realize we'll deliberate I think more extensively once we get into the specific questions that are targeted here. So don't torture yourself over it.

Okay. Rick, and then Dr. Somberg, did you have more questions or comments?

DR. SOMBERG: Let Rick go.

DR. LASKEY: Okay.

DR. LANGE: Just a follow-up on your comment, Dr. Laskey, about the patients specifically that were studied because they were younger, and our Sponsor indicated, it wouldn't want to apply this to people that may need a CRT or dual chamber pacemaker, many of which are the older population.

So in the exclusion criteria, they mentioned people that have incessant VT or need antitachycardia pacing or may need bradycardia -- have symptomatic bradycardia, and I think it would be important to make sure this isn't misused by making sure that people understand it would not be applied to CRT, patients that may be suspected need CRT or dual chamber pacing.

And the other thing to Dr. Zuckerman's point is the group that we analyze or group that have the device implanted, and as Dr. Dehmer reminded us, they were able to induce VF, they're able to get them out of VF, and they kept the device, and so that testing of the device in my opinion should occur at the time it's implanted because that's the group that we're studying.

DR. SOMBERG: One thing I'm concerned about, Warren, that you correctly pointed out is that there's a small population of heart failure here, and I forgot to ask earlier the point. So maybe we'll have a chance for the Sponsor to talk about this because now I'm anguishing myself that I forgot this, but what about pleural effusion and edema? Significant pleural effusions, edema, we see this more often in our end-stage severe heart failure patients, which I don't think you had, and that could cause impedance in the chest area or et cetera. So that may be a population to either consider studying or warning against, that we don't have that information, or maybe we have that information.

DR. BRINDIS: Another question which I know we will deliberate on is who will be the implanters because this innovative technology is relatively easy to implant, but I think that's the least issue of its application. We heard very nicely from very intelligent, smart, leading electrophysiology Sponsors talking about some of the decision making and what devices for a given patient might be appropriate, and also in terms of the management and the proper application of the device.

So it will be interesting I think for us to have that discussion. There's actually, I think, personally a disparity between the ease of implantation and the expertise required for the thought process and its proper use and its management.

DR. ZUCKERMAN: Before we lose the train of thought on Dr. Somberg's last question, does the Sponsor have a brief comment on problems with this device in CHF, pleural effusions, edema?

MR. MARCOVECCHIO: We are checking to see. I don't think we have that particular data at our fingertips to show.

DR. SOMBERG: Is there any in vitro work or any animal preclinical work? I mean just superficially --

DR. BURKE: Yeah.

DR. SOMBERG: -- water in the chest cavity would change the whole electric force fields there.

DR. BURKE: Yeah, let me -- there was an enormous amount of work in a *New England Journal* paper that's been published talking about the pre-IDE lead up to this particular device configuration, and I think what you're getting at is mostly related to defibrillation efficacy in the face of congestive heart failure, acute decompensation of heart failure. And in this particular case, if you look across the vector of defibrillation, in the left chest, whether it's in an anterior vector, in the vector that encompasses the subcu ICD today, or another study, and these are all published studies looking at defibrillation threshold, the mean threshold across multiple vectors in this left chest is about 30 J.

Specifically to the point of changes in clinical circumstance, we all have seen as electrophysiologists multiple differences in efficacy, in really sick patients, and we understand that in the development of this particular device, and that's why the start of defibrillation threshold testing efficacy was at 65 J, and the next step was to move it up even further to 80 J in order to adjust for changes in clinical circumstances.

And in this case, we don't have separated out in the follow-up at 180 day, heart failure instances that were significant or changes that would be commensurate with the answer, but I think that if you look at the preliminary testing that moved up to get to this point, I feel very comfortable as an implanting electrophysiologist that the safety margin is quite nice.

I'd like to bring up Dr. Gold just to reiterate some points.

DR. GOLD: Not so much to reiterate. I just wanted to point out that in the database there was only one patient with a documented pleural effusion and, in fact, that was documented procedure. There wasn't a pre-procedure chest x-ray. So we really don't have any data to speak of about pleural effusion. So that question, you know, remains obviously unanswered, but there was actually a very nice distribution of heart failure. So if the question is about heart failure rather than pleural effusion, in fact, a majority of patients in this study did have heart failure and there was not a predictor of any of the clinical events that we saw. So we think there was a reasonable sampling of heart failure, but I can't tell you anything about pleural effusions.

DR. LASKEY: Okay. It's mostly I and II. III, IV, I'm sure you wanted to stay away from sicker folks who might be leaning in other ways. So this population is still leaning for a heart failure population a little bit weller than --

DR. GOLD: Yeah. I mean Class IVs, we typically don't put devices into, and Class III is very enriched with CRT or bradycardia. So, again, single chamber ICDs, I think, are less frequently used in the Class III population. So, again, I would suggest that this probably is representative of the patients who get single chamber ICDs, which this device is really an alternative for, not a solution for all ICD patients.

DR. LASKEY: I think I've violated one of the fundamental tenets here. We're supposed to be talking amongst ourselves, but -- yes, Dr. Somberg.

DR. SOMBERG: Well, we seem to like the Sponsor's group of experts, too, but -- and I'm going to talk among ourselves, but it's to Dr. Gold's statement. I'm more concerned not with heart failure per se, because there's not a pathophysiologic problem so much there as with changing the thoracic impedance with pleural effusions, and that can be heart failure. It also can be pneumonia. So I mean other considerations.

So I think that could be tested. It could be tested in animal preclinical studies. It could be looked at in the registry in the future if there's a problem, but I hear, and the point is well taken that, you know, we have a margin here, but there's some people at the very ends, and I think that's what David's been concerned about, that may just be on the cusp with the long time. So we don't want that person to fall off and to -- so I think there's more work to be done on that area, and it may just be unimportant, or it may be a contraindication to its use.

DR. DEHMER: So just to follow up a little bit on what Dr. Brindis said, I mean one has to be impressed with how this is a shift in the paradigm of defibrillation therapy with subcutaneous leads. I'm impressed by what seems to be the simplicity of the insertion, but by no means is this a do-it-yourself defibrillator. There's a lot of technical aspects about this. So I heard this from the Sponsor, and I strongly support that position from the Sponsor, that this is something that, as it begins to get rolled out if the FDA approves this, really should be limited to those people who know defibrillators the best, and that's certainly the current implanters and those with special training in electrophysiology.

There's a lot that we do not know or do not yet understand about this new device. So the dilemma that we face is whether or not this new, and like I said, paradigm shifting technology is to be put out there for general use, and at the same time, not understanding all the questions that have come up from the Panel about pleural effusions, you know, I'm struck, and I don't mean to pick on Dr. Burke, but he described a patient that had the device, then went for coronary bypass surgery. The device worked fine afterwards, but I mean seriously, it's n=1. I mean we need to have more understanding about how people are going to respond after bypass, all these various variables which obviously is exactly why the PMA is being done. And, you know, that clearly needs to be done, but I think we need to approach this with some caution.

DR. LASKEY: I'll second that and third that. I mean both of us have been on white papers speaking to competency and proficiency, and so probably this afternoon we ought to specifically weigh in on the technical competence and the cognitive piece. There's a cognitive piece and there's a technical piece, and that's always been the case in this business. So we should weigh in heavily on that.

Okay. Folks, any other things rumbling around? Yeah.

DR. KARASIK: Yeah, I was just going to say that I think one of the things that struck me about reading through all this was the "simplicity" perhaps of the system because we're all, as implanting physicians, we're used to very complicated devices, and they've only gotten more and more complicated.

That being said, they offer a lot of things that are useful for the management of our patients, and so part of me, I have a little niggling concern about the simplicity of this device, and I wonder what we're giving up in some ways by offering our patients this kind of a device versus a transvenous system.

I agree that not invading the vascular system is very important, and I perceive a lot of patients that might benefit from this system. I wonder about things, for instance, remote monitoring. There's been no discussion of whether that's something that might be available with this kind of a device and how important that's become for monitoring system integrity going forward.

My sense from the storage capacity of the system is that it only stores events where the device has initiated a charge. So we wouldn't have information about non-sustained episodes. So a lot of what I do is assess patient's symptoms using sort of the Holter feature of a current ICD, and this one might not give us that ability, and so I'm just raising that as a comment.

DR. MILAN: Yeah. This goes to one of the points that Dr. Lange brought up, which is the ATP issue and trying to figure out who the right population is for this, and we haven't discussed the importance and benefit of antitachy pacing, and some people feel that recently ICDs have really become ATP devices than shocking devices. Antitachycardia pacing over the last five or seven years has become increasingly utilized even in fast VT zones and has been shown to dramatically reduce shocks and, in coincidence with that or associated with that, in some studies has been associated with improvement in quality of life, and that's simply that this device just simply can't deliver, and so the question is, you know, should it be used in patients with non-sustained VT who do tend to respond better to antitachy pacing. Should it be, you know, should it only be excluded for patients in whom they have recurrent VT for which ATP has been demonstrated to be efficacious, or is there is a larger group we should think about.

I mean it's an important question, and it's difficult to figure out how we're going to figure this out in a postmarketing setting because you can't measure the qualify of life and compare it to anybody else without, you know, sort of a head-to-head. So, you know, it's an important issue. I don't know that it needs to dominate today's discussion but, you know, it's out there.

DR. LASKEY: Well, it dominates a part of it because that's the label. So we may get there yet again. Yeah, Dr. Somberg.

DR. SOMBERG: I mean this is a fascinating discussion, and it's very interesting to hear the people who do it, you know, every day because it's a tradeoff. You're giving up some stuff. You're getting some simplicity. You're getting things that can deal with transvenous infections, et cetera. So there are positives and negatives, but that's true of a lot of medical -- it's true of all technology. I mean I have a cell phone. Someone else has a smartphone here, and you have different benefits, et cetera. So I think, number one, that's not necessarily a bad thing to have these changes. It's better to have more choices.

And I also want us to think for a minute, yes, there is the -- and I'm not sure how simple it is because it's a different type of implant. That stylus, we haven't talked about it. That looks a little dangerous, but you can do a lot of things with it, include pneumothoraxes. So you have to be cautious with that, but with that said, step back for a minute.

There is a lot of people who need a simple defibrillator, and I've read articles where those people are not being treated, and so is this the, you know, I hate to use the poor man or woman's defibrillator? I don't know how much, of course, I would say it's immaterial for us, but in a sense, this may increase its use.

So let's take a balance. Let's take a deep breath. Maybe not everyone has to be an electrophysiologist to put this in. Maybe this will change the balance a little bit more to cardiothoracic surgery. Yesterday we had all surgeons. Today we have mostly electrophysiologists. Maybe we should get them together and get boxing gloves. I would love as a pharmacologist primarily to step back and watch these things, but I just want to raise those points that there's an alternative. Not that this is inappropriate, and I do feel and I do think, yes, if this is put in everybody and supplants everything, it will be a grave mistake, a very grave mistake.

So how can we make the labeling in the manuals facilitating, but I hate to use, what was it, mandating of this because that doesn't fit every situation.

DR. LASKEY: Okay. We're getting closer to that. John -- Dr. Brindis.

DR. BRINDIS: Yeah, I want to build on that last comment. You know, there's been a lot of comments in the press related to inappropriate use of ICD implantation, and I think the real elephant in the room is under use in the appropriate population, and I think that this device may be another too with which we may be able to address underserved populations for a number of reasons, physician and patient reticence for referral related to concerns that they've been reading in the press continually related to the lead issues and whatever. So it may be that this gives us a substantial option in select patients that are suitable for this device that are not being -- with needs that are not being met.

DR. LASKEY: Rick, you have a thought about to give birth?

DR. LANGE: I was just thinking if this thing is a weapon in the hands of Dr. Somberg, we should perhaps limit it to make sure the pharmacologists don't get this.

DR. SOMBERG: I would agree with that.

DR. LASKEY: Okay, folks. I'm going to take this note of humor as an opportunity to suggest a 10-minute break, following which we come back and wrestle with the important questions posed by the Agency. We'll see you back in 10 minutes.

(Off the record.)

(On the record at 2:38 p.m.)

DR. LASKEY: Thank you again, Panel members and guest.

This portion of the meeting is now devoted to responding to the questions that the FDA has put to us, and in sequence, I will read the background for the question, and then we will deliberate amongst ourselves.

So our first question is directed to safety, and for those who don't have the script, I'll just read the background.

The primary safety endpoint, the complication-free rate at 180-days post-implant, was assessed in all patients with an attempted S-ICD System implant. The 95% lower confidence bound was 97.9%, which was above the performance goal of 79%. If the non-evaluable patients are counted as failures, the performance goal was still met with a lower bound of 91.7%.

While the primary safety endpoint was met, there were 48 adverse clinical events reported for the delivery of therapy when it was not required (that is, 48 episodes of inappropriate shock). 30.6% of shocks that occurred during the follow-up were deemed inappropriate (including in the denominator the 41 shocks that were unconfirmed in a VT/VF storm in a single patient). These events can be divided into two categories: shocks for SVT with ventricular rates above the programmed shock rate zone threshold (and there were 20 patients); and shocks resulting from inappropriate sensing (and there were 28 here). FDA's review of the literature suggests that approximately 1/3 of all shocks are inappropriate in a similarly indicated population with transvenous systems. FDA notes that the device has the ability to provide a maximum of approximately 21 shocks for the delivery of therapy over a 5-year life of the device.

So the first question directed to the safety endpoint is please discuss whether the incidence of inappropriate shocks for the S-ICD System is acceptable. Specifically discuss how the limited service life of the device impacts this assessment.

What I'd like to do here is just to gather some consensus which I will attempt to summarize and see if that satisfies the Agency's needs. So do you want to weigh in on 1a here, incidence of inappropriate shocks, is it acceptable or not? And discuss the impact of limited service life on this number.

DR. MILAN: I'll jump in and say that I think that the incidence of inappropriate shocks for this system is acceptable, and I was pleased to see that dual zone programming further, well, it further appeared to reduce that. Obviously it wasn't controlled or anything, but it seemed to have a pretty big impact, and so I wasn't -- I mean there's -- talk about tradeoffs. I mean it's just the cost of saving somebody's life is every once in a while you get an inappropriate shock, and this has been true for transvenous systems as well. So I was not concerned about the rate of inappropriate shocks.

And the second part is how the limited service life of the device impacts its assessment. I frankly have not been impressed by the limited service life of this device. I should phrase that more clearly. I have not been concerned by the limited service life of this device.

I still tell my patients when I implant an ICD in them that they should expect it to last for four to six years. I'm talking about transvenous ICDs, and then we're pleasantly surprised when the devices live longer than that. So I was not concerned about either of these two issues.

DR. LASKEY: Good. Let me get Pam. I missed her. Sorry.

DR. KARASIK: No, no, I would voice the same opinion. I think that the frequency of inappropriate shocks is very consistent with what we already see in the current transvenous era, and I think that the service life is also consistent with what we're used to telling our patients. I would say that if you choose your population correctly and you use this as a primary prevention device, the vast majority of our patients actually fortunately don't ever need the device, and the devices have a four to six, seven year battery longevity. And so I think if you could give three shocks a year for five years, you'd be ahead of the game. I think that's perfectly okay.

DR. LASKEY: It also is true, is it not, folks, that with the discussion we had about dual zone programming, that that may impact positively the rate of inappropriate shocks. So it would have a positive benefit.

Okay. So to 1a, I would summarize to the Agency as saying the consensus here seems to be that this is an acceptable rate of inappropriate shocks and that it does not appear to be, at this time with this data in front of us, any indication of limited and an adverse limitation.

DR. ZUCKERMAN: Thank you. That's quite helpful.

DR. LASKEY: 1b related to safety -- will somebody put up the 1b. It asks us to discuss whether the totality of the safety data provides valid scientific evidence in establishing reasonable assurance of safety of this device, a corollary to 1a, but it still requires an answer.

Dr. Somberg.

DR. SOMBERG: I think it does, and I'm especially reassured by the clinical data. While the testing was less than what had been desired in planned testing in vivo, the spontaneous events supplemented that, and that was very helpful, and I think with the assurance that there's going to be a postmarketing study to collect additional information, I think we are well on our way to establishing safety of this device.

DR. LASKEY: Okay. So with those caveats, Dr. Zuckerman, that is that the data at hand has a relatively small number of patients out at 150 days to speak to this point, and certainly the postmarketing survey construction or study construction would take this into account, but at the moment, we have an affirmative to 1b.

DR. ZUCKERMAN: Okay. That's quite helpful. Do any of the electrophysiologists have any further questions or concerns regarding the totality of the safety data?

DR. MILAN: Just a qualification. I think -- well, maybe I misheard it, but I think Dr. Somberg, you were talking about testing the device and spontaneous episodes, which in my mind is the efficacy of the device, not its safety. When I think about the safety, I think about the implants and the complications that were associated with that, and I think the data demonstrates safety insofar as it was explored, so with the two qualifications that Dr. Laskey mentioned.

DR. ZUCKERMAN: Thank you.

DR. LASKEY: Yeah, the OPC were set, and they were vested, but the OPC figure may actually change over time as the device matures.

The second question relates to effectiveness. The study assessed the effectiveness of the device for treating induced VF at implant in 314 successfully implanted subjects. The 95% lower confidence bound of the successful conversion rate in the 304 evaluable subjects was 98.8%, meeting the performance goal of 88%. If the non-evaluable subjects are counted as failures, the performance goal is still met (with a LCB of 91.7%). In addition, 71 out of 74 evaluable subjects had successful 65 J VF conversion testing at 150 days. The 3 cases that were unsuccessful at 65 J were all successfully converted at 80 J.

The trial was not specifically designed to capture a large number of spontaneous VT/VF events. However, there were 120 instances of spontaneous VT/VF captured in the IDE (that is, there were 68 of those) and the OUS registry, the outside the United States registry (there were 52), all of which demonstrated successful device function.

So please discuss whether the data provided regarding induction testing, in combination with the spontaneous episodes documented both in the IDE and the OUS registry, provide valid scientific evidence that establishes a reasonable assurance of effectiveness of the device for detecting and treating tachyarrhythmias.

You probably want it to be ventricular tachyarrhythmias.

Rick.

DR. LANGE: I think it does, and again I would just like to reiterate that the induction testing at the time of implantation was an important part of this trial, but the combination of that and the follow-up, both with spontaneous and recurring induction more than 150 days afterwards, gives me reasonable assurance of the effectiveness.

DR. LASKEY: As a naive participant, I would think that the real-life data, the long-term data, spontaneous VT/VF is fairly convincing, too, but obviously could be increased in number with the post-approval study.

Dr. Somberg, did you have any --

DR. SOMBERG: I agree completely with you.

DR. LASKEY: Dave.

DR. MILAN: So this, as you know from my comments already, this is where I'm still struggling. You know, I've already pointed out that the performance goal of 88% to me is not what I would accept clinically in that while, by the Sponsor's definition, when you censor those patients who are non-evaluable, then you get 100% efficacy at implant testing.

The problem is that censored patients in the clinical world don't just disappear. You have to do something with those patients, and it's not the job of the clinician and the patient to give the device a fair shot of defibrillating under whatever rigorous, stringent testing is pre-specified; it's the job of the device to convince the physician and the patient that it's going to save their life if they're called upon.

And so I don't know exactly how to handle non-evaluable subjects, but at least 7 of those and probably 11 of those should be considered induced conversion failures, and so I'm still struggling a little bit with admittedly small numbers, the problems there, and my initial concerns about the follow-up VF induction testing were addressed by the Sponsor, Dr. Gold.

I mean underlying my concerns is the knowledge that transvenous ICDs, we know a lot about them. They've been around for a long time; in part, work by Dr. Gold and others have informed us that they work exceptionally well. We know what happens to defibrillation thresholds over time. We know exactly what the safety margin needs to be. It's a tough field in which to enter, and so, you know, that's what I'm struggling with, is that we know relatively little about this new system, and how do we convince ourselves that this is -- I mean I admit that there are tradeoffs because there are clear advantages to a non-transvenous system, but if the tradeoffs start to appear to impact patient safety, then I think that's where I'm struggling.

DR. LASKEY: John.

DR. SOMBERG: Yeah, I appreciate your comments, and they have been very informative and very expert and that, but let me take you through this for a moment. It met its agreed upon performance standard, and we have to have some respect because if we don't set some goals and things, then nothing could ever be approved, and we will end up with you having a lot of frustration when you treat your patients, one.

Two is it never failed, correct me if I'm wrong, when it was called upon to do just what you said, to save a life in the real world. Now, we have very small numbers, and that is a problem, and that's why we're not, at least I'm not opening my checkbook, and I don't think, you know, the regulatory will open their checkbook and say just use it, you know, here it is. We follow it. We do that. So it's never failed.

And, second of all, some of these situations, you know, whenever you do studies, there's always things that don't fit in, you know, the peg is not perfectly round, and it doesn't always and there are awesome outliers, there's awesome things that don't fit in, but you can't explain, and that's what I think they got here.

So, yes, you're right, but I don't think you're correct in saying that therefore this is not an approvable device based on efficacy. It did meet its efficacy standard, it never failed, and those two things are important, and this Sponsor has provided such detail, you know, they've done everything they could. So it's not if you do a messy study, you have a lot of loose ends and they can obfuscate. This is not the case here, and I think they will be delivering on that follow-up data. So those are reassuring things.

And that's why I would say prove me wrong because I'm willing to be proven wrong here.

DR. LASKEY: Maybe Dave -- well, Dr. Zuckerman, the consensus up here to a large degree is that, yes, the data did provide assurance regarding effectiveness, and the study was designed to beat a "relative easy target." There are still some unresolved issues which should be looked at in post-approval, but on the whole, I think we have a likely assurance or an assurance of likely effectiveness. Would that language, that Bayesian language make you a little happier? I mean we're not 100%, but we're certainly in the high 90s, and I think the consensus up here is that this is an effective device.

DR. ZUCKERMAN: Okay. I think the FDA has heard a good discussion where there's a reasonable assurance and the device did meet its primary effectiveness endpoint, but I'd like the three electrophysiologists to look at FDA slides 62 through 64, because I do want to go back to the key point that Dr. Milan made, which is the electrophysiologist has to see real-world patients and estimate an acute effectiveness endpoint, and although the Sponsor did calculate primary effectiveness of a prespecified protocol, what is the method of calculation that helps you the most in figuring out what is acute effectiveness here and how you would decide whether a patient is an appropriate candidate? Would you include all three calculations, or what's your sense here of how this device really operates?

DR. KARASIK: Okay. I'll jump in. So speaking as purely as a clinician here, I think, it is my personal feeling that you have to look at the worst-case analysis when you're thinking about what's the best thing for your patient. Slide 64, assuming 17 failures is giving an estimate of 94.7%, which obviously still meets the performance goal.

I think part of what you're hearing is that we know with a transvenous system, if the device fails at implant testing, there are things that we can do to improve the system at the time of implant to at least guarantee as best we can that the device would work. We can move the lead. We can add other components to try to get a system that works.

One way to look at this is to say we're willing to place a subcutaneous system. We will test it at the time of implant, but if it fails, we're taking it out, and that's a little bit of a paradigm shift in thinking about how we implant devices, but this may require thinking about it in that way, that you go in with -- we think you're a good patient for this device. If it doesn't work, we're going to transfer you to a regular transvenous system, and you'll be on the table a little bit longer, and that is how I would think about it going forward, but I would use the worst-case analysis. I think that is really the honest one.

DR. KELLY: You know, I think that's probably what I would do, too, but I'm not sure scientifically it makes a lot of sense because if you look back to the early days of defibrillation threshold testing, it wasn't a couple of shocks, and we called it a threshold. You started high and you went down, down, down, down, and then you failed and then you went back up. So because I would worry, I might do that, but I think we're not entirely right taking one failure and calling it a failure because that isn't a real defibrillation threshold.

DR. MILAN: So I like slide 63 because from what I gather, these six non-evaluable results that didn't have any failures were one with a ventricular thrombus and five were VF, could not be induced in a sustained fashion. So that does happen, and it's difficult to know what to do with those patients, but this is the slide I like for, if you wanted me to say what I think the primary effectiveness endpoint is from a clinical perspective.

DR. ZUCKERMAN: Okay. So those comments are very helpful because we've asked three electrophysiologists who are quite distinguished, and we've gotten three different results. So it helps the FDA just make a decision, which is that the three analyses all have value added, and we would consider putting the three analyses in a label with appropriate explanations. Thank you. Sometimes we do, and sometimes that's helpful also.

DR. LASKEY: I'd like to move on to indications, the third question.

The IDE clinical study enrolled all patients with Class I or Class II indication for a ICD by societal guidelines who had an ECG deemed appropriate per the ECG screening tool. Based on the findings of the IDE study, the Sponsor has proposed the following indications for use:

The S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, do not have incessant ventricular tachycardia, do not have spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing.

So the first question under indications is, considering the demographics of the patient population studied, discuss whether the proposed indications for use are appropriate.

Dr. Somberg.

DR. SOMBERG: They seem appropriate. We haven't discussed a specific group that we would specifically, you know, we wouldn't take away these caveats here, and I don't think there are any distinct exclusionary groups that have to be inserted there was as well. So there are some loose ends like the pleural effusions, et cetera, but that may be chest wall abnormalities, deformities, things of that nature, but I don't think that needs to be put in here. Those are things that the physician will evaluate.

DR. LASKEY: Starting with Dr. Brindis.

DR. BRINDIS: I'm comfortable with the way it's written in terms of these patient subgroups, but at the same time, we heard the Sponsor's experts talk about patients who deserve a device where a transvenous CRT would be better therapy, and even implied by the Sponsors themselves to imply that the overall subset of primary prevention might be a smaller group than the way the indication is written. So I need some help and guidance in how to acknowledge a patient subset that would be better served with a different device as opposed to the way this is written. I'm unclear on how I would suggest that be done.

DR. LASKEY: Rick.

DR. LANGE: I echo Dr. Brindis' comments. But the patients that would need either a dual chamber of pacing, a different device might be more appropriate and CRT as well. So some way that the FDA could work with the Sponsor to make sure that those patients are directed towards a different device preferentially.

DR. LASKEY: John.

DR. SOMBERG: Wouldn't those considerations be more appropriate for potential exclusions from the -- see, the way they're trying to word it, is they're trying to focus in that this is for VT/VF, but it's not for incessant, it's not for bradycardia and, you know, some very key points because of the way the device is engineered, et cetera. So I mean it's six of one and a half a dozen of the other. I wouldn't argue with you, but I think we're getting into the smaller stuff. I can see how someone could get this device and 4 or 5 years maybe, 10 years later, needing a CRT, and maybe this would be explanted and a new CRT-D in the patient at that point. So you have to be careful what you write because then it becomes exclusionary, and if you ever do something in another court of, you know, federal law or something, somebody reads this and get into all sorts of problems.

DR. LANGE: Well, in fact, that's what happened because there were a couple of patients had VT storm, and you couldn't predict ahead of time. So I'm less worried about it happening down the road and saying, well, things have changed and a different device would be more appropriate. So that doesn't concern me as much.

DR. LASKEY: To this prediction point, I think that's a good point. Something I struggled with is that, well, the device is really for those who are going to need infrequently, primary prevention more in this study than secondary prevention, but how do you predict? Are they going to need it infrequently? What is infrequent? And what's out there in terms of an evidence base to help us fine-tune the indications for use; those that were low risk, I don't know. I think the state of the art is really pretty crude right now in terms of risk stratification, but would any of you consider taking that further in the label, saying at low risk of an event? It'll happen sometimes. We don't know when. We don't know how frequently, but they need it.

DR. LANGE: Warren, for the reason you mentioned, I just don't know who's going to be at low risk and high risk yet unless it's already occurred, and I'd even go to the point of saying if they're having frequent VT, even if it isn't cured by antitachycardia pacing, I'm not sure this is the best device just because of the short life. That is, people that have frequent episodes, even if it's not terminable by antitachycardia pacing, are probably better served with a transvenous system.

DR. LASKEY: So bringing us full circle back to the question, for this patient population, the population studied in this analysis, are the IFUs appropriate? We think so, Dr. Zuckerman. However, it is likely that the target population as it's described will be different going forward, will likely be older, sicker, perhaps with more advanced comorbidities, and so there will be some element of fine-tuning, again those most in need of this device.

DR. ZUCKERMAN: Okay. And that's fine. It's just that technically when the voting occurs, we do it once, and we will be voting on this indication statement. Again, my question to our electrophysiologists, are they comfortable with this indication statement? For example, it does rule out Dr. Lange's concern right now of frequent, recurring VT. It also covers the symptomatic bradycardia issue as well as incessant VT.

So are there any other suggestions here?

DR. MILAN: I think the need for biventricular pacing is the other one. If you're going to put bradycardia in there because it required a different device, I don't know why you wouldn't also put meeting current indications for biventricular pacing.

DR. KELLY: I agree that something about frequent ventricular tachycardia should be in there. I just don't know how we define that and what frequent is, but, you know, certainly personally if I had somebody with monomorphic ventricular tachycardia, maybe even one episode, but definitely more than that, I would put in something. Just because you can't pace terminate them now doesn't mean you won't be able to pace terminate them down the line when they're on an antiarrhythmic drug or after they've had an ablation, but I'm just not sure how to say that. Maybe put that in exclusions or considerations or somewhere.

DR. ZUCKERMAN: Well, those are all good points, Dr. Kelly, and we do use the warnings and precaution section to further explain, or we can use the warnings and precaution section to further explain the intent of our label.

Similarly, you know, Dr. Milan, with regards to patients who are in, you know, Class III heart failure, not responding to optimal meds, we can indicate that this is not the intended pathway.

DR. LASKEY: Nor was it in the sample population study. So we're leaving you with a probable yes for 3a, but with all these other dangling concerns.

DR. ZUCKERMAN: Okay.

DR. LASKEY: Anything else? No.

And then for 3b, discuss whether there are additional subgroups of ICD-indicated patients who should not receive this system, should not.

Well, I'll begin the patients that were not in this study, patients that weren't included should probably not be on the indication for use. So, again, advanced heart failure comes to mind most frequently.

Anything else?

DR. KARASIK: Well, they didn't include patients with advanced renal disease, and I would not want to see that as an excluded group. So I would be a little careful about -- I think the CRT comment is a reflection of this as well, and that that's appropriate, but I wouldn't want to exclude patients with advanced kidney disease. They are a niche that might do very well with this kind of device, and they were excluded from the trial.

DR. LASKEY: John.

DR. SOMBERG: Well, let me play devil's advocate. We exclude people because they weren't in the trial with advanced heart failure. And by the way, as rightfully pointed out, people are putting in these devices less and less with Class IV heart failures. So, in fact, none.

But let's take someone in New York Heart Class III heart failure or someone who needs a CRT, but they've had an episode of endocarditis, maybe they have, you know, other problems in that regard, and you think it is better to have an external, you know, less mechanical things in the heart you have. So there are instances here. So I would be careful. I would put, you know, warnings, precautions, considerations. There's a large label. Unfortunately most people don't read a large label, but with that said, there's a lot of place to put these things, and I think even pleural effusion, because it wasn't tested, and there's a pathophysiologic potential, but I wouldn't want to say it as a categorical exclusion. I raise caution. I think the way it's worded here is for the indications covers a lot of the major things, and everything else is a little bit more speculative maybe.

DR. ZUCKERMAN: Okay. And I would ask the Panel members to consider this question, the philosophical spirit that Dr. Somberg just mentioned because that's really the type of advice that we're requesting. In fact, if you go to Section 7.1, page 5, there's really only one contraindication. It's a standard and well-founded contraindication for this type of system, but the other issues that have been raised, as Dr. Somberg points out, are more in the warnings and precautions arena.

DR. LASKEY: Greg.

DR. DEHMER: So, again, this may be perhaps a little controversial, but I'm just going to throw this out there for the group to comment on, but if you left the indication just as it is written, where you're excluding people with the symptomatic bradycardia, the incessant VT, or the VT that responds to antitachycardia pacing, but at the very end, you put on an additional thing and said in whom a traditional intravascular device would be problematic, I mean I have very vague wording, but it would restrict it I think a little bit. It would make people stop and think about whether or not they should use a traditional transvenous device or whether this would be an alternative. It would put some burden of responsibility on the physicians to be thinking about it, but I mean I guess I'd rely on the electrophysiologists here. Would that wording be helpful? Would it be too restrictive? Would it be confusing? Make no difference whatsoever.

DR. LASKEY: I guess I'm uncomfortable with using problematic in an indication for use. It really doesn't help either way. So somebody who recommends patients for this procedure, I know what you're grappling with, but I think leaving it as vague as it is before we started may not be helpful.

DR. ZUCKERMAN: That's correct, Dr. Laskey. We generally don't use the word problematic in our indications for use.

DR. DEHMER: Well, you could use a different word but --

DR. SOMBERG: I know what my colleague is getting at here, and I think if anything, the lead investigators for the Sponsor were -- took the lead in that area. So I'm less concerned about and I defer to the responsible individuals, you know. It's not the universe of all physicians, but you're responsible for the most part, and it's a very small universe of people they put this in, and I think if things are clearly delineated in the other areas that we've talked about, because people don't have the time to go through a briefing book and spend hours discussing this, but if these warnings and precautions are listed, I don't think we have to put it so far up front, and I think most of the electrophysiologists understand that, you know, if you need -- there's going to be resistance against this. If you need a CRT system, you're not going to use this. If you need antitachy, you're not going to use this. They feel fine. It's like trying to introduce a Smart car when everyone's driving Chevys and the Mercedes and, you know, Fords, et cetera. So the Smart car has made sense in very large cities where you can park it in your living room if you need to, but this is -- I'm not as concerned as maybe as you that this will be overwhelming use; I'm trying to present the other side of the coin. I think there's going to be more resistance to its use.

DR. LASKEY: Okay. Only one other thought comes to mind about a group that should not receive. Are we comfortable with hypertrophs? They were really not a large part of this study, and yet it's a large problem. Should we exclude them or just leave this as is?

DR. LANGE: There were a few hypertrophs.

DR. LASKEY: Very few.

DR. LANGE: There weren't that many.

DR. LASKEY: There weren't that many.

DR. LANGE: I'm going to echo what John said. I don't think we can exclude people that weren't in the study, I mean just as with stents where they were for de novo, small, discrete lesions, and their use expanded to figure out where they were or weren't particularly beneficial. So I would not favor restricting hypertrophs.

DR. SOMBERG: Just to bore you with another point is, you know, Brugada Syndrome, and people with T wave, all sorts of abnormalities, et cetera here. I mean we start getting into the weeds on this, but people who have identified the need for this understand that, and they're going to incorporate this. So I just wouldn't put these things up front. There are some concerns about hypertrophic cardiomyopathies you might have as well, but once again, the people are going to be looking at this who are the inserters, and I don't think they need that wake-up call at this salient level of the indication.

DR. LASKEY: Okay. Then it's say fair to say the Panel has not really come up with any other groups who should not receive.

DR. ZUCKERMAN: Thank you.

DR. LASKEY: Okay. Moving onto the label, question 4.

The labeling for this device includes the indications statement that you just reviewed, information about the device, the user's manual, the patient manual, and the physician's training program. The purpose of the labeling is to describe the functionality of the device and how to use the device.

So please discuss whether the proposed label is acceptable or whether modifications are recommended. Consider, discuss whether the labeling should describe differences and limitations of the device compared to transvenous ICDs.

Rick.

DR. LANGE: Yeah, to me the labeling seemed appropriate. Describing differences I think is fine. I think when you describe limitations, it ends up being a problem. We don't ask any medication described, the limitations compared to other medications or other drugs or with other devices as well, and those things change by the way, and some of it is perception and some of it's easily documented. Some of it's not. So I don't want to get into -- I don't think we ought to be in the business of saying let's compare limitation of this device against every other device or every other technique. I just think that's going to be particularly burdensome, and you can't do that unbalanced without saying these are the benefits as well if you're going to do that.

DR. LASKEY: But leaving the differences in the label. So don't get into the limitations but leave differences.

DR. LANGE: In particular, letting people know that it doesn't provide CRT pacing. It doesn't do bradycardia pacing. So that someone doesn't put it in with unrealistic expectations of what it does.

DR. LASKEY: Okay. Anything else?

DR. SOMBERG: Well, I don't remember the -- you know, I went through this a couple of days ago. So I'm not going to say I'm mixing this up, yesterday's thing as well in my head. So -- but I do think there's a whole host of discussions here today that we had of -- I mean everything from using the dual mode to the potential that we don't know what pleural effusions do to the situations where using the initial screen is important. There's a whole host of things that I think need to be covered here and we talked about, and I don't remember the patient manual's discussion of the tone and battery life and other aspects, and these are things that should be -- you know, we brought it up today, and I think someone has to go through and look through this thing in more detail again. And I apologize, but I can't remember all the comparisons.

DR. LASKEY: Did we hear today that the patient manual and/or the physician training program were still under modification, or have we seen a stable, at the moment, stable end product?

MR. MARCOVECCHIO: Certainly some of the things that were discussed today are still under development. One example would be the best way for us to describe how the use of dual zone programming has the potential to reduce inappropriate shocks.

DR. LASKEY: So I would include that as one of the modifications obviously that you don't have in front of you at the moment, but going forward, that would count.

DR. ZUCKERMAN: Okay. Our general practice is I think there was a good interchange between Dr. Lange and other Panel members and the Sponsor regarding some labeling changes that would add value, and we do traditionally go through the Panel transcript carefully with respect to those prior comments. It sounds like there aren't any additional comments that people have come up with at this time.

DR. LASKEY: I think that's fair to say. Then onto physician training.

The S-ICD System is designed to be implanted without fluoroscopy and does not require transvenous access. However, VF induction and testing is an important part of the implant procedure. The physician must ensure that the device can detect and treat a tachyarrhythmia at implant as well as during long-term follow-up. In the IDE study, all implanting physician investigations had privileges to implant transvenous ICDs. The Sponsor also provided data demonstrating that physician training was essential in reducing the number of complications and observations experienced during the IDE study.

So we are to comment on the specific types of medical training or experience that are most important for physicians who will be implanting the S-ICD.

I'll just lead off where we left off before the break, which is that in areas of invasive cardiology, of which I guess this is still a part, competency and proficiency are the hallmark of the day, and so therefore technical and cognitive competence and proficiency need to be verified objectively or demonstrated objectively and maintained. So how should we go beyond that wording?

DR. SOMBERG: I'm going to take a bit of a controversial stand, that I think it's a training procedure manual, and whatever else has been worked out between the Sponsor and the FDA to evaluate and to see if a person has been trained and thus certified to implant this device. I think that's what should be based as those who can do it, not necessarily if you're an electrophysiologist, a cardiothoracic surgeon, or interventional cardiologist.

You know, I've spent my life at teaching hospitals. The only person who's going to do this is going to be an electrophysiologist, but I can see people 100 miles away, and maybe a cardiothoracic surgeon, who does pacemakers, et cetera, but there are fewer of those.

Okay. With that said, but I can see 100 miles away or in a primary care center, I can see someone who specializes in pacemakers doing this, and it may not be an electrophysiologist. So -- but that doesn't mean that that person can't be made competent in the decision making, both implanting it and evaluating whether the device works. Also evaluating whether they need it or not.

DR. DEHMER: So I'm probably not in complete agreement with that. I think as I said before, this is not a do-it-yourself procedure. You know, I can maybe look forward and, should this device be approved, look into the future of 5 or 10 years from now, at areas which are underserved by electrophysiologists, perhaps not in this country but maybe in other areas. This device is alluringly simple to put in. I mean it really is, and that's attractive, and that means that there are maybe many other individuals who need such a device who are not getting such a device because of the complexity of the existing devices that are approved.

So I could see 5, 10 years from now, where the indications, in terms of who could put this in, would be greatly expanded, and perhaps there would be physicians that would go through the appropriate training, of course, that might be allowed to put this device in, but I think at the present time, there's enough that we don't know about this device and the nuances of using this device that we really need to have our most experienced and thoughtful individuals be the ones that are dealing with this device and putting it in, and certainly at a major medical center, that more than likely will be an electrophysiologist, but I don't think that that is uniformly going to exist.

So I think at least at these initial stages, it probably needs to be restricted to those that have the most experience and knowledge base, cognitive base because I think the technical skills are not that demanding.

DR. KELLY: I would agree with that. I mean I think we've left the labeling and the indications fairly vague. If you look at the NCDR Registry, 22.5% of devices got put in for non-traditional indications, and it was 35% by cardiac surgeons. So I think if we're going to leave the labeling vague, which I would agree with, I think we have to limit, at least initially, who puts them in.

DR. KARASIK: I would just say that an ICD is an ICD, whether it's transvenous or subcutaneous, and although it may be technically a far simpler procedure, the ability to induce, treat, and deal with ventricular fibrillation in the lab is certainly different than putting in a dual chamber pacemaker, which a lot of our colleagues do who are not trained as electrophysiologists. So I would be in favor of for now at least limiting the device to physicians who have whatever we decide the appropriate training is, but I would say it should be electrophysiologists at the moment.

We don't really know how this device is going to perform in the long term, and I think we need to be a little cautious in that regard.

DR. LASKEY: Yeah, I think we're heading towards a consensus that irrespective of how seductive this is, I mean there's a hazard in being seduced. This is more than just implanting. This is implanting and being responsible for follow-up as well as all the cognitive base of this discipline. So I think we're weighing in on, with all due respect to Dr. Somberg's point, we're weighing in on a demonstrated competency and proficiency and may as well stay within professional societal guidelines. Do you -- --

DR. LANGE: A question of my esteemed electrophysiology colleagues, and I may get three different answers here, but just for my benefit, would you allow cardiac surgeons that are currently putting in ICDs to put this device in? Just a yes or no.

DR. KELLY: Well, if 35% of them don't meet the indications, I don't think so.

DR. MILAN: None of the cardiac surgeons at my hospital do that. So I really don't have a basis for making an opinion on that point.

DR. ZUCKERMAN: Okay. I think this has been a good discussion where it's been pointed out that in addition to just the technical ability, there is a strong need for a knowledge base, and that really requires having appropriate people put this device in even if you can do it very simply.

The interesting thing is that some of the actual guidelines and requirements extends beyond the FDA's authority as to what can be done at a particular hospital, but we can certainly put in the labeling and work with the Sponsor to appropriately identify the type of training and experience which is necessary, and it does sound like the consensus of the panel is to be cautious in this or at least staged.

If I have summarized things incorrectly, please let me know.

DR. LASKEY: I think that's quite correct, Bram, and you're really knocking on 5b with that. I think that addresses or at least approaches the training issue.

Perhaps there's another word for implanting because again it gives the connotation that those who do this can walk away from it having implanted it, and we want to send -- there's a more meaningful aspect to this, not just implantation. So maybe the Agency could wordsmith this.

DR. MILAN: Selecting and inserting.

DR. LASKEY: Yeah, some indication of pre-procedural judgment, implant, and post-procedural responsibility or aftercare.

DR. MILAN: Pre-procedural selection, implantation, programming, and testing.

DR. LASKEY: Okay. To 5b, to the training aspect.

Consider the impact of the learning curve on the clinical events reported (and there clearly was a learning curve demonstrated here). Please comment on the S-ICD training program proposed and provide any additional recommendations for this training program.

Okay. It's fair to say we haven't seen the whole training program. I mean it's still a moving target. There's other pieces of the dual zone programming that agreeably have to be included into the user manual and the training program, but other instances of --

DR. LANGE: Yeah, it's interesting. I'm not sure there's a learning curve as much as there's an experience gained from this. I mean this is -- as my colleagues said, this is incredibly simple. I can do this in the garage. I don't even need fluoro, but I've got to keep the front down so it stays sterile.

So I didn't see it as a learning curve as much as an experience of how to manage it and program it. In that respect, it was different I think than many other more complicated devices.

DR. LASKEY: Okay. Probably not helpful, but I interpreted this to mean, for example, the discovery at the investigator meeting that dual zone programming significantly mitigated the rate of inappropriate shocks. I thought that was an example. You know, you get better as you do more, and here's why.

DR. LANGE: Well, but again I guess I'm interpreting a learning curve differently, and that is that with an individual site or an operator, they get better at this particular procedure, but I don't think the procedure necessarily changed. I just think as we gained experience, we knew how to program it, which I think is very different, probably the only experience.

And the other thing again is the small number of infections wasn't -- it was again an experience curve rather than a site or investigator learning curve. That's the distinction I'm making.

DR. LASKEY: All true. John, I'm going to say something. I'm agreeing with you here, but the pneumothorax issue. What if in the next 500 cases there were 2 pneumothoraxes? I mean so I think that there's a learning curve here any time you do anything manipulatively or mechanically that they've recognized and addressed.

Beyond the buffing up of the dual zone, are there any additional recommendations for the program that we can pass on to the

Agency?

DR. KARASIK: I think one of the points about the learning curve is the prepping of the patient is substantially different, and I actually was a little concerned about the number of superficial infections, and I think that's a function in part, as we've heard from the Sponsor, about teaching your lab about how to prep a patient. I think I have, as we say, enough gray hair to remember when we first started putting transvenous ICDs in, in the EP lab, and the infection rates were much higher because there wasn't the same level of comfort as you had in the operating room for prepping a patient. So I do envision significant training having to happen within your lab and within your staff before you start putting these devices in.

And I think the other issue is this, although it's simple, how you tie this thing down and how you secure it is actually quite important because there were a number of lead movements and leads that had to be repositioned, and you've got to learn how to do that so that the thing doesn't move.

DR. BRINDIS: So I'm not sure how appropriate it is to have a training program where you actually talk a little bit more about patient selection in terms of the device in addition to the actual mechanics of utilization of implantation of the device and programming and whatever. Maybe this is part of the aspects of responsible diffusion of an innovative technology to help guide the upcoming implanter to be better selective in their patient use.

DR. LASKEY: I agree, Ralph. I think this harkens back to the language that we just quickly crafted for you to supplant implanting with pre-procedural decision-making judgment. I think that speaks volumes to that point. I agree. It's as important as prepping the patient, if not more.

So is the Agency inclined to change the wording of implanting to something more robust?

DR. ZUCKERMAN: Yes, such that it'll be understood that the training program involves more than just the technical knowledge for acute implantation. There's a whole battery of steps and thought processes that need to be incorporated for optimal use of this device.

DR. LASKEY: That would be 5b.

Moving on to query 6. Overall benefit/risk.

The IDE study for the S-ICD System highlights the risks and benefits of the device which have been reviewed here throughout the day. The primary benefit of the device is that the S-ICD System implantation does not require placement of an endovascular lead. Prominent risks of the device include inappropriate shocks, and in comparison to transvenous ICDs, higher rates of infection, increased time to delivered therapy, and reduced device service life.

So please comment on whether the benefits associated with the S-ICD System outweigh the risks.

John.

DR. SOMBERG: I take a little exception to the way this is worded because I think it slants things.

First of all, higher rates of infection. We talked about that. There are different degrees of infection, and having a transvenous system infected is a major problem ,and having this superficial. So that's one thing.

Increased times of delivery, I heard that and we debated it -- you know, I don't want to use the word debate, discussed it and -- but there was no clinical sequelae as pointed out by the Sponsor. There was no syncopes, albeit small numbers and inappropriate shocks. I tend to agree with Dr. Milan here that, you know, it's -- the middle is the most appropriate, those six patients left out, and I think the number of inappropriate shocks can be looked at different ways. So I think this is an extreme here.

With all that said, I think the benefits clearly outweigh the risks here, not to minimize them and not to say that a postmarketing study isn't going to be requisite.

DR. LASKEY: Rick.

DR. LANGE: Warren, the paper published yesterday showed that if you have an implantable cardiac device, your in-hospital mortality is 15%, 14.7%. And so I agree with John. The way this is worded almost slants it like this is a high-risk infection. I'm not sure that's true, but what I am certain is there weren't any in this small group of patients, admittedly small, that there wasn't any serious infection, and certainly doesn't carry the mortality of the current cardiac devices.

So the answer is, yes, I think the benefit outweighs the risk.

DR. LASKEY: Right, and again I agree with you here. I mean perhaps something a little less objectionable, higher overall rates of infection but with small rate of serious infection, would be more truthful, that these infections were easily managed or relatively easily managed compared to bloodstream infections and site implant infections.

DR. SOMBERG: We just should say that we sound to each other extremely loud. So we apologize, but I was afraid I was yelling, and when I hear him, even though he says he agrees with me, it's like ringing in my ears. So I don't know what's going on here. Maybe the sound mixer people can help with the acoustics here, but we do apologize.

JOHN: Mr. Chairman, if we could make sure that everyone speaks directly into the microphone and gets fairly close, we can get something that's consistent. That would help us out greatly.

DR. LASKEY: Fair enough.

JOHN: Thank you.

DR. LASKEY: Okay. Any more on risk/benefit, folks? Yeah, Dave.

MR. MILAN: I agree with several of the comments so far in that I'm not concerned about inappropriate shocks or higher rates of infection compared to the transvenous ICDs.

The part that I sort of sound like a broken record here, but the issue of undersensing ventricular fibrillation and resulting increased time to delivered therapy gives me pause, and it would be mitigated by the lack of syncope in the clinical experience, if the clinical experience were larger.

DR. LASKEY: Well said. And we'll bring that forward on the next question I guess.

So, Dr. Zuckerman, I think we've weighed in with a consensus here that there is demonstrable positive benefit-to-risk ratio.

DR. ZUCKERMAN: Thank you. Does that include Dr. Milan in your final summary? I mean you disagreed with some of the prior comments, but when you add everything up, do you agree with that final assessment of benefit to risk?

DR. MILAN: Are you asking for my vote now or --

DR. ZUCKERMAN: No, we're not. We're asking for your discussion and viewpoint right now because it is different from some of your colleagues'.

DR. MILAN: Yeah, so that's -- Bram, I haven't, to be perfectly honest, I don't know exactly how I'm weighing these things right now, and the issue is that syncope is not to be underestimated as clinical importance in these patients. There's no way that you're in VF for 20 seconds and you haven't passed out. So when I see that in the -- it's bigger than that, right. So when I see that in the induced VF episodes, that 10 to 12% of the patients had episodes that lasted greater than 18 seconds, those patients if they had VF would certainly have syncope as outpatients.

And you could say, well, let's pick that up in the post-approval study. If you ask an ICD to tell you how long the episode takes, but the problem was it wasn't sensing the episode, you may not get an accurate picture of how long that episode really took. So I'm not sure you can pick this up.

And then an additional question is what about completely undersensed VF episodes that don't end up getting a shock at 30 seconds but end up not getting treated at all. And so those look like sudden deaths, and even if they're small numbers, they're significant. I mean, you know, we're talking about the ultimate endpoint here.

So I don't know how to say it any other way. I'm just really concerned about this ventricular fibrillation undersensing with this device and, you know, I'm not concerned much about the risks. I'm just worried about whether the efficacy of this device is really up to par with what the clinical standard is right now, which is transvenous ICD.

DR. ZUCKERMAN: Okay. Those are very important comments, and as you've pointed out, the goal of question 6 is not to take a vote but to get everyone thinking about the key issues because I do just want to indicate one important point. When a vote is taken in a short while, we have to vote on the data that we have, not the data that we have and additional data that might accumulate in a post-approval study one year down the road. Thank you.

DR. LASKEY: All right. Okay. Dr. Zuckerman, that would be our summary.

DR. ZUCKERMAN: Thank you.

DR. LASKEY: All right. To post-approval study, question 7.

The proposed post-approval study for S-ICD System is an observational registry consisting of patients initially implanted with an S-ICD System in the IDE clinical study and an additional prospectively enrolled cohort from approximately 50 U.S. clinical centers, for a total proposed minimum enrollment of 650. The primary purpose of the proposed post-approval study would be to demonstrate the 36-month S-ICD System complication-free rate. Complications felt to be associated with the S-ICD System and mortality would be collected. However, data on electrical performance, battery performance, and safety and effectiveness questions such as shock efficacy, inappropriate shocks, infections, and chronic pain or discomfort would not be collected. Study data would be collected and entered into the NCDR ICD Registry and analyzed at predetermined intervals identified in the post-approval study protocol. FDA would like the panel to consider the following questions regarding the post-approval study.

So to discuss the adequacy of the proposed post-approval study, let's look at bullet number 1, whether acute safety and mortality is sufficient or whether effectiveness and chronic safety data should be collected as well.

Do we have any -- yeah, Dr. Naftel.

DR. NAFTEL: So I think there's an important distinction we need to make before we start. There's so many registries going on now that the hospitals are really struggling, and I just look at our hospital with the STS database, we have a group of nurses, intelligent people, abstracting data from medical records and putting it into databases, into STS. So it becomes a very passive system, an observational system.

So that my question is under the way this study is headed, can it be a group of data extractors that can pull out the data that we want, or will it have to be a nurse monitor who is funded and who is devoted to this study, regardless of whether it's through the NCDR database or not, but it's a real question. Is this a passive study, or is this an aggressive proactive study. And I don't know the answer from what I've heard.

DR. LASKEY: Dr. Somberg.

DR. SOMBERG: I think we've discussed this, that it's going to be a mixture of the two, and I think that's what the Sponsor was alluding to as well because the acute data is important, but we have concerns. I don't have a concern that it's insurmountable at this point for risk/benefit assessment and approval, but I have a concern in the future that we need more data. We only have 16 real-life situations that we can look towards. So that has to be obtained.

So I think you use, what is it, the NCDR Registry. You add to that. Clearly that has to be quality assured by the Sponsor if it's going to be presented to the FDA. So I think there's going to have to be that component as well, and I think when we go through each of these things here, we're going to add a little something else. So I would say whether acute mortality is sufficient or whether effectiveness and chronic safety data should be collected, and I was going to say, you need chronic safety data and you need effectiveness data.

So long-winded response is I think a passive collection of data that's in the NCDR database is just not going to be acceptable.

DR. LASKEY: Okay. So on the premise that we need accurate surveillance, passive surveillance isn't going to do it, so active surveillance should certainly include a number of elements, and I guess we'll add to the bullets as we go forward. But we all agree at least with the first bullet that chronic safety data as it's defined in this study -- should we modify that to include any other endpoints since it says as well?

UNIDENTIFIED SPEAKER: I don't --

DR. LASKEY: First bullet, whether acute safety and mortality is sufficient, which we have weighed in and said no, and whether effectiveness and chronic safety data should be collected as well. So are there other chronic safety data measures that you would like to see?

DR. ZUCKERMAN: And in helping you with that part of the discussion, perhaps you could look at FDA Slide 74 to see if those are some of the appropriate endpoints that might be considered.

DR. LASKEY: Okay. Ralph.

DR. BRINDIS: Well, we actually have sort of a slight disconnect because if we talk about safety, infections are part of safety. One of the challenges with the NCDR being a, you know, a procedural hospital-based registry is some of the infections will occur after discharge, and so unless we have some mechanism, in terms of a more active surveillance related to infections, that would be an added value, then I think part of the component of safety we won't have.

DR. LASKEY: But we need.

DR. BRINDIS: But we need. Thank you for finishing the sentence.

DR. LASKEY: John.

DR. SOMBERG: That's certainly true, albeit that if it becomes a serious infection, you usually get your way into a hospital, unless you're a nutty doctor who refuses to get admitted and gets his IV at home or something, but with that said, I agree with you and maybe we should make a list of things because I think, you know, Slide 74 is very useful, battery life is certainly important, the lead performance and adverse events such as infection, whether people with severe heart failure, edema, and pleural effusions cause a problem, and I think we talked about five years for follow up, and I think we talked about the performance. Maybe that's in the next question, and I shouldn't go onto that. Okay. Sorry.

DR. LASKEY: I guess the point here is there's -- simply because the NCDR's mostly limited to acute implantation and shortly thereafter, that should not limit us in our thinking, and that there are ways to link databases. You have to construct a database following hospital discharge to get this, but there's ways to link what goes on in the hospital with what we need here, which is long-term.

DR. ZUCKERMAN: Correct, Dr. Laskey. So I think what would be helpful to the FDA is to forget the NCDR a moment. That might be one mechanism, but to first hone in on what are the critical acute and chronic safety and effectiveness endpoints that need to be monitored. What are critical hypotheses, and then the Sponsor and FDA could develop mechanisms, but we really need some help on figuring out first what are the questions that need to be answered in a post-approval study.

DR. LASKEY: Okay. Folks, so we can develop a list here for the Agency, but acute mortality speaks for itself. I don't think we need to really dwell on that. Other measures of acute in-hospital or peri-implant procedural safety would be?

UNIDENTIFIED SPEAKER: Infection.

DR. LASKEY: Infection. Two?

UNIDENTIFIED SPEAKER: Failure.

DR. LASKEY: Okay. Failure. Three?

UNIDENTIFIED SPEAKER: Inappropriate shocks.

DR. LASKEY: Would that be an acute -- I guess that could be acute. All right. Inappropriate shocks.

So similar to what we're seeing in the PMA, but there are others such as, if we expand this to other anthropometric subsets, we're going to have pneumothoraxes. We're going to have errant placements. So I think we should look at other, as in infection and pneumo come to mind, bleeding comes to mind.

DR. BRINDIS: Well, I appreciate us generating a wish list, although I can say that most of the things that we just talked about in terms of procedural implants, the implant process itself will be picked up by the registry. So I'm sort of thinking a little bit after the discharge, in terms of the wish list as opposed to worrying about the in-hospital procedural complications.

So infection came to the list, and in terms of David's concerns about long-term efficacy and what was just mentioned, inappropriate shocks, that information, you know, we were sort of looking at that with our present five-year study. So that can be done with interrogation of the device and adjudication of shocks. Again, that would be not what the NCDR does. It's in-hospital, but that might be on the Panel's and FDA's wish list in terms of assessing long-term efficacy and inappropriate shocks, and actually it seems pretty doable.

DR. LASKEY: And that would be down at the third bullet level, Ralph, but we'll get to that. Rick.

DR. LANGE: Conversion to a transvenous system.

DR. LASKEY: Yeah, I guess I disagree with Dr. Brindis. I don't see where we can discount acute procedural safety measures. Oftentimes they're a predictor of subsequent badness as well. Patients who fare poorly upfront may fare poorly down the road. So we should get some measure just as these investigators have done.

DR. BRINDIS: I think you misinterpreted me. I said that will be a given with the registry. So we'll have that data.

DR. DEHMER: I think we had presentations about all the testing done on the lead, but you'd certainly want to track ongoing assessments of lead and lead failure. What are the parameters and impedance and so forth over time for this lead, so that maybe you can hone in a little bit more precisely on what's going to be the estimated lifespan of a lead.

DR. LASKEY: Dr. Kelly.

DR. KELLY: I think we've talked about syncope, and that may be important. And the other thing that we didn't talk about today, I think about a 5% incidence during induction of the shock inducing atrial fib, which is not something we commonly see with transvenous devices. I think during induction it wasn't a big deal, but it could be something that induces atrial fib, and then they get a whole bunch of shocks after. So maybe we should make sure to look at that when we look at inappropriate shocks.

DR. LASKEY: So what I'd like to do here at this point is just to combine the second and third bullets here. The second bullet is whether a 36-month follow-up duration is acceptable, and the third, whether a complication-free rate performance. So we're talking about longer-term safety. So we should agree hopefully that we want 5 years, 60-month data for the Agency. Are we all -- yeah. So we all seem to agree with that.

DR. SOMBERG: And the performance should be higher. And the performance, we talked about many times, shouldn't be 79% at this point. This is -- we're up to 94%, you know, on that Panel, you know, a lot of us agree on. So I think we should talk in the high 80s, even higher than that at this point to be looking at.

DR. LASKEY: Well, we can let the Agency and the statisticians dwell on that. I think that has a lot to do with the sample size. I think tossing out a number of 650 has no immediate basis for it, but there would be a basis for a more formal prospectively defined p0, and that's up to the Sponsor and the Agency, which target are you aiming for and how did you get there is something that's not going to be resolved today, but is necessary to have a prospectively defined hypothesis. Would you accept that?

DR. ZUCKERMAN: Yes. So that the performance goal at five years needs more work, and that's the general drift today.

DR. LASKEY: Anything else on the additional chronic safety measures or acute for that matter?

Good.

Should there or are there additional subgroups which should be analyzed in addition to gender that should be required in the post-approval study?

Yes, sir.

MR. DUBBS: I may have made this point early on, but I think that there needs to be an affirmative, conscientious effort to increase the number of women that are in the post-approval study and the number of minorities. Regardless of the fact that these registries and the percentages are comparable to what the numbers were and what we looked at earlier today, I think that we need to develop more information and more data on women and minorities and the use of these devices and the results.

DR. LASKEY: Okay. That's a good point. Many registries have oversampled women and minorities. So there shouldn't be a reason not to do that here. I think that's a valid point. Any other subgroups? Dave.

DR. NAFTEL: So another way to look at this, and the way I look at it is, on the really important endpoints, both safety and efficacy or effectiveness, if all of those are submitted to intelligent, physician-driven, multivariable analyses, with the understanding that it's not just a multivariable analyses to come up with a table, but to actually be used to find groups that aren't doing well, for example, putting in body surface area -- whatever, and find and actually doing an investigative analysis to say, okay, this works really well in these types of patients, not as well in these or these patients are at higher risk. So I'm saying a more sophisticated version of a subgroup analysis, but do more than essentially anybody does with multivariable analysis; actually turn it into something clinically relevant.

DR. LASKEY: Dave, to that point, I should just point out that you can't do that stuff without having all the data. You can't have missing data. You've got to get all the variables entered. So I think that was implied in your opening comment, but it's nice to do explanatory regression, but you need all the variables.

Greg and then John.

DR. DEHMER: In terms of other subgroup analyses, I think if I'm recalling the data presentation, you had more people for primary prevention than second prevention, and you had a predominance of people who, for lack of a better term, were not quite as sick and other things. So I think you'd want to do a subgroup analysis on the effectiveness in primary prevention versus secondary prevention and also based on, I guess, the level of sickness of the patient.

DR. LASKEY: Yeah, not to rediscover the wheel, but ischemic versus non-ischemic, you know, that would be helpful.

John, did you have a comment?

DR. SOMBERG: Well, just a caution. We don't want to put too much into it because it increases error and serendipitous findings that are -- So, but with that said, I just wanted to point out, especially to our Patient Representative, that you have to have a pathophysiologic -- and this is one of the instances where I don't think, you know, hormonal or genetic differences will make a very big different in terms of response. So minority groups or women, but I think it's more on body surface area, you're small or you're large, and I think also the pediatric population because we're talking that there may be some reports in pediatrics. This may be a problem, may not be. So that's another subgroup to look at, in fact, we haven't discussed today. Is this going to be -- is there an age indication or body size cutoff that's going to be recommended, and these are questions that I don't know if we have to address today, but it's questions the FDA does.

DR. LASKEY: Okay. Whether testing to address long-term tissue damage should be incorporated into the post-approval study, particularly for those receiving multiple shocks. So assessing long term, I guess if there wasn't any evidence of short-term, there may not be a reason to really look, since everything costs money. Do we agree with this?

DR. SOMBERG: I was just saying, how do you measure long-term tissue damage?

DR. LASKEY: I don't know, John. Area under the curve of CPK. I don't know. These guys looked at CK, and they looked at other measures of tissue damage acutely.

DR. SOMBERG: Just -- that's the right word. It's acutely but after, you know, you get 10 shocks --

DR. LASKEY: Right.

DR. SOMBERG: -- you measure it a year later, you're not going to see that. So you have to measure myocardial viability. You have to do a perfusion scan. That's going to be -- that almost will equal the cost of the defibrillator insertion.

DR. LASKEY: So there are a lot of people shaking heads here. I don't think that we would add this to this list.

Okay. Are you okay with answers 1 through 7?

DR. ZUCKERMAN: I'm okay.

Dr. Wei, do you have any final questions?

No. So we're all set. Thank you.

DR. LASKEY: Okay. At this time, the Panel will hear summations, comments, or clarifications from the FDA.

DR. ZUCKERMAN: Mr. Shein, did you want to add any final comments?

MR. SHEIN: Good afternoon. Mitchell Shein again. I think that we've heard a good, robust discussion of the questions that we've laid out for you. You had some good insight. We certainly have some footwork that we will need to be going back and doing with Cameron in the aftermath of today's meeting, but I don't think we have any other further comments.

Bram, do you have anything else that you can think of?

DR. ZUCKERMAN: No, I don't.

DR. LASKEY: Other summations, comments, or clarifications from the Sponsor? And you have up to 10 minutes. Thank you.

MR. MARCOVECCHIO: Just very briefly, I wanted to thank you, Dr. Laskey, and the rest of the Panel for your attention today. As you heard from Mr. Shein, you heard two very consistent presentations today. We presented a study that clearly met its primary endpoints, and additional data from other sources that provided further support of the product, and we've been working on this system for more than 11 years. We're committed to this technology and convinced that the system provides a viable means to treat life-threatening ventricular tachyarrhythmias in a new way without the use of a transvenous lead.

And so I'd just like to close by thanking the FDA Review Team and thanking the Committee for this opportunity to talk about the S-ICD System, which we believe is a new alternative for treating patients in need of ICD therapy. Thank you.

DR. LASKEY: And to echo the sentiments up here, thank you. This was really a pleasure to work through and deliberate with you. Thank you for a very clear presentation.

Before we proceed to vote, I would like to ask our Consumer Rep, Industry Rep, for their opinions. So I'll ask Mr. Dubbs, Burke Barrett, and Ms. McCall, our Patient Representative, if they have any additional comments. Mr. Dubbs.

MR. DUBBS: Thank you. I think the presentations were excellent. I view the device as very elegant, innovative. The technology is incredible. I think it's effective and safe, but not to belabor the point, I don't agree with Mr. Somberg, Dr. Somberg. I think there needs to be some more study of women and minorities, and it needs to be broken out into a subgroup and not just based on a percentage of 24, 25, 26%. I think it should be much higher.

DR. LASKEY: Ms. McCall.

MS. McCALL: I'd like to thank the Sponsor and the FDA for a very clear and thorough presentation as well as answering some very complicated questions. I'd also like to thank Ms. Williams for coming in and explaining and giving her explanation and her experience between both ICDs that she had had. I found that very interesting.

My role as a Patient Representative is to take this huge notebook they send to me, read through it, and then listen to the combined decades of experience sitting on this Panel, and boil it down to risk versus benefit for a patient. As someone who has heart issues, who's actually had tachyarrhythmia and syncope, don't do it at the grocery store, I think this is a big step forward. We need competition, and I think we need a step forward, and what it boils down to is, would I recommend this to family and friends? Would I have this? Absolutely, yes.

DR. LASKEY: Mr. Barrett.

MR. BARRETT: Thank you. It's been a remarkable day, and I say that for me because I can't help but juxtapose and compare and contrast today's meeting to some of the other meetings at this Panel over the last 18 months or so.

We saw in the FDA slide this morning that the pivotal study was started in February of 2010, that the data cutoff for the data that was reviewed today was Valentine's Day, February 14, 2012, and we're sitting here some 10 weeks or so later. Now, I understand it was an expedited review product and the follow-up was six months, not a year, but still compared to other recent reviews, there's about a five-year time period from when the study is solidified to when we're here reviewing the data, and I think that's a reflection of the company, the clinicians, and the FDA doing the work upfront to design a well-designed study.

We're here talking about a study where the endpoints were OPCs, and that hasn't been a topic of conversation. It wasn't a randomized study. Apologies to Dr. Naftel. It wasn't compared to a registry. It was an OPC study, and it was by all regards and by the review today well designed and well conducted.

So I want to say to my colleagues in industry to look to today for examples of what we can do or how it can be done, and I want to, you know, close by paraphrasing the FDA Branch Chief who stood up and said that both sides of the aisle are in agreement, that that is the ideal goal I think for industry of this process. Thank you.

DR. LASKEY: Thank you. Okay. With the Panel and group's indulgence, we are now ready to vote on the Panel's recommendation to the FDA for this PMA. The Panel is expected to respond to three questions relating to safety, effectiveness and risk versus benefit.

Ms. Waterhouse will now read three definitions to assist in the PMA voting process.

MS. WATERHOUSE: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency.
The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - There is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

DR. LASKEY: So the Sponsor has proposed the following indications for use statement.

The S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, do not have incessant ventricular tachycardia, or do not have spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing.

So we will now proceed to the vote, and Ms. Waterhouse, will you go through the voting procedure please.

MS. WATERHOUSE: Please locate the handheld remote. For the next three questions, press 1 to vote yes, 2 to vote no, and 3 to abstain. Please be certain of your response before you select your answer. Once a selection is made, there will be no opportunity to change your vote.

Before we begin, we will take a test vote to verify the voting devices are working properly. So please press 1 for yes, 2 for no, 3 to abstain.

(Panel vote.)

MS. WATERHOUSE: We'll move onto question 1: Is there a reasonable assurance that the Cameron Health S-ICD System is safe for use in patients who meet the criteria specified in the proposed indication? 1 for yes, 2 for no, and 3 to abstain.

(Panel vote.)

MS. WATERHOUSE: Okay. The poll is now closed.

I'll read the second question. Is there reasonable assurance that the Cameron Health S-ICD System is effective for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WATERHOUSE: Okay. The poll is now closed.

We'll move onto question 3. Do the benefits of the Cameron Health S-ICD System for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WATERHOUSE: Okay. The poll is now closed.

I will now read each Panelist's vote for the record.

Okay. For question 1, Dr. Naftel voted 1 for yes. Dr. Somberg voted 1 for yes. Dr. Milan voted yes. Dr. Brindis voted yes. Dr. Karasik voted yes. Dr. Dehmer voted yes. Dr. Lange voted yes. Dr. Kelly voted yes.

For question 2, Dr. Naftel voted yes. Dr. Somberg voted yes. Dr. Milan voted no. Dr. Brindis voted yes. Dr. Karasik voted yes. Dr. Dehmer voted yes. Dr. Lange voted yes. Dr. Kelly voted yes.

And for question 3, Dr. Naftel voted yes. Dr. Somberg voted yes. Dr. Milan voted no. Dr. Brindis voted yes. Dr. Karasik voted yes. Dr. Dehmer voted yes. Dr. Lange voted yes. Dr. Kelly voted yes.

Please give us a moment so we can tally the votes.

On question 1, the Panel voted 8 to 0 that the data shows that Cameron Health S-ICDs are safe for use in patients who meet the criteria specified in the proposed indication.

On question 2, the Panel voted 7 to 1 that there is reasonable assurance that the Cameron Health S-ICDs are effective for use in patients who meet the criteria specified in the proposed indication.

On question 3, the Panel voted 7 to 1 that the benefits of Cameron Health S-ICDs outweigh the risk for use in patients who meet the criteria specified in the proposed indication.

Please pass the voting devices to the end of the table for collection. Thank you.

DR. LASKEY: At this point, I'd like to ask the Panel members to discuss their votes. Particularly if you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference. So I'll begin with Dr. Brindis.

DR. BRINDIS: Thanks, Warren. Again, I want to also congratulate the Sponsor and the FDA for terrific presentations and my fellow Panelists for a great discussion.

I actually believe that this device is a substantial additional adjunct in the tools for electrophysiologists to manage patients who are at high risk for sudden cardiac death. The opportunity to be able to have a device in particular to manage patients who have infections of transvenous systems is a very important adjunct in the armamentarium.

The issue of patient and physician lack of referral for appropriate patients for implantation, particularly for primary prevention, related to concerns of lead failures, rational or irrational at times, this device may offer opportunity for this device to be available, important therapy for populations that are underserved. So those are my comments.

DR. LANGE: Again, my appreciation to the Sponsor for doing a very well done study, to having excellent follow-up, for very clear presentations and transparency. And it gives me great confidence that the Sponsor will both define the appropriate training and the appropriate patients in whom this technology should be applied.

And my appreciation to the FDA as well for a very thoughtful and very thorough presentation and for the expedited review, and as Burke mentioned, this is a great example of how the cooperation between industry and the FDA should work.

This is an example of what I call ISHTOT technology, I Should Have Thought Of That, and it's really elegant and simple and, as Ralph said, I think a great addition to what we have available. So it was a pleasure to actually review this.

DR. SOMBERG: I concur with my colleagues' statements. I was impressed by the technology. I thought it was an excellent undertaking by the Sponsor and a very thorough and good FDA review.

I think the operational word here is "reasonable assurance" of safety and effectiveness. We have an expedited review. We have a small patient population. I believe it is reasonable. I hope I'm a biomedical scientist, and I'm willing and always open to findings opposite of my conclusion.

With that, I want to say I have a lot of respect for my colleague, David Milan. I hear his comments. I've been in a minority position before, but I think the coherence of the work, the ability to compare to a comparator and the real-life situation all give me reasonable assurance, but I do hope that Dr. Milan's concerns which are based on excellent insight and mechanical engineering, electrophysiology is looked at very carefully because just by doing a slightly less than good follow-up on this, that could be missed for years, and it's going to be very difficult to discern, but even if this -- so that's all very important.

But my final comment is, even if this device is not equal or better than the transvenous systems, it will define large number of patients that really need it, and that's one of the other reasons I felt compelled to put that on. So I do have confidence that the Sponsor will not try to see this, because of the ease of insertion, to just supplant very good therapies, but to expand and provide utility in those people who have problems with the transvenous systems.

DR. DEHMER: I won't belabor things because I agree with everything that has been said by the previous speakers. The key word for me was "reasonable assurance," and I feel reasonably assured that this device is safe, that it is effective, and that it will meet the criteria for the proposed indications. So that was the key thing for me.

We don't have all the answers yet on the use of this device, but I have confidence in the Sponsor and the Agency that they will pursue those answers and, you know, if it turns out that this is not the perfect device, you know, I'm perfectly fine with that. It is an alternative device, and I think that is its greatest value at this point in our understanding about how to use it.

DR. KELLY: I'll just echo the comments about the reasonable assurance of safety and efficacy, and I also think this device meets an unmet need for a small but definite cohort of patients.

DR. KARASIK: I think this is something a lot of us have been waiting for, for a very long time. We've all recognized the need for a non-transvenous system, and so I do think it's very exciting to have this innovation and hopefully to have it out there.

I agree with what everybody said, and I really think only time will tell whether or not it's embraced by the electrophysiology population, whether we actually adopt using it, and I think in a relatively short period of time, we're going to know whether this works for our patients or not, but it's been a fascinating experience, and thank you.

DR. MILAN: So I want to echo Dr. Brindis' hope that this device will rejuvenate enthusiasm for a field that has been plagued by repetitive reports of device recalls and malfunctions, and it's my hope that this device will do that and get the patients who have a clear indication for defibrillator but haven't been treated yet into our offices so we can help them.

However, I felt that we should balance our enthusiasm for this novel technology with a cautious approach that would ensure the efficacy meets what we've come to expect as a standard in the field, and the standard is quite high for transvenous systems, and so I remain concerned about undersensing of ventricular fibrillation and delays in time to therapy on that basis, and in addition, I think that the number of patients in the IDE and the relatively short duration of follow-up could not assuage those concerns.

DR. NAFTEL: So I'm always fascinated when the Panel or anybody medically says that something's okay because it's like something before. So just the inappropriate shocks, say it's okay because it fits in with what exists, it's always amazing to me that we do that and a little bit surprising. So to me that's not a good thing. It's a place to work.

However, that's got nothing to do with the way I'm thinking or voting. I'd like to thank the Sponsor and the FDA for a really nice process. The FDA's comments were so good. The whole regulatory process just really worked this time. I'd like to thank the Sponsor for a well-designed study, a well-implemented study, wonderfully analyzed and just superbly presented.

And the thing I want to thank you for the most is not once today did anybody say the word "propensity" or "imputation." So thank you for that.

DR. LASKEY: I would ditto everything that's been said. I really had a lot of fun today. As Mike Gold knows, I'm an amateur electrophysiologist. So this was really a lot of fun to see how this field is moving.

I would leave the Sponsor and Agency with one other thought. I currently care for the majority of folks in New Mexico with adult congenital heart disease. This is a burgeoning population. A lot of them, most of them have sick hearts by the time they're 30 years of age, and not all of them are transplant candidates obviously. So this is a wide open area for a very useful, even if it's a niche area, for further development as you go forward.

But, again, on behalf of all of us, thank you, and to my Panelists, thank you for indulging me and allowing us to sort of move forward efficiently here today. I thank you all.

Finally, I'd like to thank Dr. Zuckerman for putting up with us as he always does and reminding us what our path is, and I would ask you if you have any final comments.

DR. ZUCKERMAN: Yes. Number one, I want to thank Dr. Laskey and the Panel members for supplying FDA with extremely fine advice and comments today.

Since we do have a few minutes left, I'd like to see if we can generate just some additional comments on another niche population that might be served by this device, and was touched on briefly by Dr. Somberg, but I'm wondering if the electrophysiologists have any additional comments.

Specifically, this system hasn't been evaluated for pediatric use yet, and that's appropriate noted in the label on page 5, but if the Sponsor was encouraged to do a study in the pediatric population, are there some suggestions that people around the Panel have that would make this a doable study given the difficulties of doing studies in pediatric populations?

DR. KARASIK: It's awfully large to use in a smaller pediatric population. So there might have to be some size considerations to the kind of patients you would use it in.

DR. LANGE: Both for the device and the lead since it's a one-size-fits-all lead. So lead size considerations or length as well.

DR. KARASIK: Right.

DR. SOMBERG: That's the challenge to the Sponsor because I don't think it would be this device. We were having a little side discussion on pediatrics before. I don't think it would be this device in the smallest of the small, and where there's a need because of growth and change, et cetera, but, you know, engineering is engineering, and you have a problem, you guys will solve it, and if you can't solve it, you call back Steve Jobs and he'll make you solve it.

DR. LANGE: Bram, with regard to the fact of children growing and leads not being able to have a lead that's easily extractable, and you don't have multiple different leads in the venous system is very attractive. So if the Sponsor would like to take this on, it would be at least with my enthusiastic support.

DR. ZUCKERMAN: Okay. Thank you.

DR. LASKEY: This meeting is adjourned.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

April 26, 2012

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

____

CATHY BELKA

Official Reporter